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Occupational Exposure To Styrene: Contribution To Hearing Loss

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OCCUPATIONAL EXPOSURE TO STYRENE:

CONTRIBUTION TO HEARING LOSS

by

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ABSTRACT

Prolonged significant noise exposures are well known to result in permanent hearing loss. However, little is known of the contribution of industrial chemical exposures to hearing loss. Information available, both from animal and human studies, raises the possibility that certain aromatic hydrocarbons are ototoxic. The purpose of this study was to assess whether occupational styrene exposure causes hearing loss in a group of workers in the fibre reinforced plastics manufacturing industry. The hearing acuity of 299 subjects was determined, using pure tone screening audiometry, at the beginning of a single workshift and again at the end of the shift. On the same day, the personal, time-weighted average exposures of each subject to both styrene and noise were measured. In addition, information was obtained from each participant on factors including: previous work history, including exposures to noise and chemicals; use of personal protective equipment for noise or solvents; personal and family history of hearing problems; and, smoking history. Current exposures, together with work histories were used to construct lifetime noise and styrene exposure indices.

No important relationships were observed between styrene exposures and changes in hearing acuity over the course of the workshift. Therefore, styrene does not appear to exert an acute effect on hearing, at exposure levels which were generally within the current standards. Similarly, no conclusive evidence was found for a chronic styrene-induced effect on hearing acuity, when both noise and styrene exposures were taken into account. As expected, age and noise exposures were highly important variables, both positively associated with hearing loss. In addition, the detrimental effect of

noise exposure on hearing acuity was found to be strengthened with increased age, suggesting a synergistic effect. Noise and styrene exposures were highly correlated, clearly illustrating the importance of considering all associated variables in analysis of such data. No conclusive evidence was found for a relationship between smoking, recreational noise, other solvent exposures and hearing loss. Further, the study highlighted the difficulties in constructing retrospective exposure indices when actual, historical measurements are lacking and reliance must be placed on alternative methods such as questionnaire responses from individual subjects.

In loving memory of my father

Dr. Andrew Sass-Kortsak

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CHAPTER 1: INTRODUCTION

It has long been recognized that prolonged, significant noise exposures can cause permanent hearing loss. Almost all industrial workers in Canada are potentially exposed to excessive noise levels and, in Ontario alone, it is estimated that there are approximately 4,000 claims per year to the Workers' Compensation Board for noise induced hearing loss.[1] It has always been assumed that hearing loss in the workforce, other than that associated with age, was related to excessive exposure to noise. Very little is known of the contribution of chemical exposures. However, recently it has been suggested that exposure to certain chemicals might also produce the same debilitating disease. Information available both from animal and human studies, raises the possibility that certain aromatic hydrocarbons, for example styrene and toluene, are ototoxic.

The purpose of this study was to assess whether occupational styrene exposure is associated with hearing loss in a group of workers in the glass fibre reinforced plastic manufacturing industry. Styrene exposed workers were chosen as opposed to toluene or xylene exposed workers for two reasons. Industries where a sufficiently large group of workers are exposed to toluene or xylene, as in the paint manufacturing industry, usually involve exposure to a wide variety of additional organic solvents including methylene chloride, varnish-makers and painters (VM and P) naphtha, varsol and others. On the other hand, in the fibre reinforced plastics industry, workers are exposed primarily to one aromatic solvent, styrene. Secondly, the use of this industry

and the styrene solvent allowed for direct comparison with a recent similar study[2] which suggested an ototoxic effect of styrene.

In 1981 it was estimated that approximately 1000 Ontario workers in the reinforced plastics industry may be exposed to styrene on a continuous basis over a full shift.[3] The total number of workers potentially exposed to styrene in Ontario was estimated in 1980 to be around 8,000.[3] The number of workers exposed to other aromatic solvents such as toluene and xylene is even larger. Therefore, if aromatic solvent exposure does in fact contribute to hearing loss, either through a direct effect or through synergism with noise, this could have serious implications in devising control strategies to prevent hearing loss and workers compensation criteria. At the present time control strategies consist of either engineering controls to reduce noise levels in the workplace or the provision of hearing protection. Should there be a contribution to hearing loss from solvent exposure, these control strategies may not be wholly protective.

1.1 Glass Fibre Reinforced Plastics Manufacturing Process

Styrene is the major component of a resin which, when applied to strands or woven sheets of fibreglass, polymerizes, to create a rigid plastic material. The fibreglass, bonded into the rigid polymerized resin, provides strength. Glass fibre reinforced plastics are used in the manufacture of items such as boats, storage tanks, pipes, tub, whirlpool and shower units, truck camper tops, car parts and trays. These items are

typically manufactured in either the manual *open or contact molding* process, or, the more complex *closed molding* process.[4] *Closed molding* processes include match-metal die molding in which the resin and fibreglass mixture is placed between two dies and temperature and pressure are applied to aid in the curing process.

The *open molding* process involves a reversed (female) mold of the item to be manufactured. This is generally sprayed with a wax, followed by a pigmented resin (gel coat) which contains up to 40 percent by weight monomeric styrene, and will ultimately appear as the outer surface of the item. The item is manufactured by laminating alternate layers of fibreglass, as strands or woven sheets/cloth, and resin. A variety of methods are used in laminating. In hand lay-up, resin is sprayed, brushed or rolled onto the fibreglass cloth. As the mixture cures, the surface is rolled to ensure saturation, eliminate the air bubbles and excess resin, and shape the item against the mold. Hand lay-up can also be accomplished using a "chopper gun" which sprays the resin, mixed with chopped strands of fibreglass, onto the mold. Hand rolling is required to compress the mixture as it cures. Items such as boats, truck and camper tops and tubs and shower stalls are made in this manner. Pipes and tanks are generally manufactured using filament winding, where continuous strands of fibrous glass pass through a resin bath and are wound, wet, on a rotating spool or mandrel. Rollers are again used to remove air bubbles and excess resin. In the present study, all but two of the participating plants used *open molding* manufacturing processes which are generally associated with higher styrene exposures.

1.2 Study Objectives

The overall objective of the study was to determine whether an exposure-effect relationship between hearing loss and styrene exposure existed. The specific objectives were:

* to determine the relationship between styrene and noise exposures, and change in hearing acuity over the workshift; and,
* to assess the relative importance of noise, styrene, age and other factors in the prevalence of hearing loss in the subjects.

This was accomplished by identifying glass fibre reinforced plastics manufacturing plants willing to participate in the study and determining the hearing acuity of each participant on a single workday, at the beginning of the workshift and again at the end of the shift. On the same day, the personal, time-weighted average (TWA) exposures of each participant to styrene and noise were measured. In addition, information was obtained from each participant on his previous work history, particularly exposures to noise and chemicals, personal and family history of hearing problems, use of personal protective equipment, such as ear muffs/plugs or respirators, smoking history and other similar questions.

CHAPTER 2: LITERATURE REVIEW

The term organic solvent covers a broad range of substances from many different chemical classes with highly diverse chemical, physical and toxicological properties. Organic solvents have found widespread use in industry since the middle of the last century and many of the toxic effects associated with exposure to these materials have been described. A variety of organs can be adversely affected by exposure to solvents, the nature and magnitude of the effect depending upon the solvent, the level of exposure and the frequency and length of exposure. However, nearly all solvents will exert an effect on the central nervous system (CNS). Inhaled solvents are rapidly absorbed from the lungs. They are usually highly lipophilic and easily enter and are retained within the lipid-rich nervous system. Acute overexposure to some solvents has been shown to result in CNS depression, not infrequently with a fatal outcome.[5]

2.1 Neurological Effects of Chronic Occupational Exposure to Solvents

Over the past two decades, much investigative work has focused on the neurophysiological and neurobehavioural effects of chronic, low level exposures to various organic solvents. This scientific inquiry has been primarily centred in the Scandinavian countries and in Great Britain. Much of the work has examined occupational exposures to a variety of individual solvents and to solvent mixtures.

Most studies have been conducted on workers chronically exposed to organic solvents. For example, in a study of industrial spray painters, reported by Elofsson *et al*,[6]

statistically significant differences were found in tests of memory, perceptual speed, reaction time and manual dexterity, as well as in several neurophysiological measures, between a group exposed to organic solvents and two industrial control groups.

Cherry *et al* examined two groups of solvent exposed workers (44 exposed to paint solvents and 52 exposed to toluene) and age-matched nonexposed controls for a variety of neurobehavioural effects.[7] The study showed few effects that could be related to solvent exposures: a slight excess of minor clinically demonstrable peripheral nervous system deficits. No differences were observed in neurophysiological measures of peripheral nervous system function. According to the investigators, their most interesting finding was the lack of subclinical deficits in performance tests, a finding in contrast to previous studies, including that by Elofsson.[6] In their study, Cherry *et al* originally found apparent deficits in a series of performance tests; however, these disappeared when proper corrections were made for differences in pre-exposure intellectual capacity in the two groups. The authors speculated that such differences in inherent intellectual ability may not have been taken into consideration in the previous studies.

There have been reports in which effects have been measured by decrements in performance in a series of psychological and psychomotor tests. These included memory disturbances, impaired judgement, speed of response, comprehension, headache, signs of peripheral neuropathy and changes in evoked potentials. These

studies, although generally highly suggestive of neurobehavioural and neurophysiological deficits associated with solvent exposure, are far from conclusive. Several studies[7-11] have been unable to demonstrate any effects attributable to solvent exposure. Further, those studies with positive findings varied widely in the type of effect shown. Psychological dysfunctions[12-21] have been described in some, while in other studies psychomotor deficits[6,12,22-26] have been shown. There are a number of limitations, collectively, in these studies which may explain the lack of consistency. With the exception of three studies,[11,24,25] the exposures were to a broad mixture of organic solvents, often a combination of aromatic hydrocarbons, for example toluene, xylene and styrene, chlorinated hydrocarbons, for example perchloroethylene and trichloroethylene and aliphatic hydrocarbons, for example n-hexane, as well as alcohols and others, for example carbon disulphide. A review of experimental (animal) studies has demonstrated that different organic solvents have diverse neurotoxic effects and also that the toxic mechanism may differ between chronic and acute exposures.[26]

In studies of a clinical nature[12,15,19,20,27-29] the subjects were actively seeking medical help for a suspected neurological disease due to solvent exposure, thus making it difficult to draw etiological conclusions.[10] In nonclinical studies, exposure to solvent was classified in some according to job title, duration of exposure or interviews with subjects,[7,11,16,18] while in others attempts were made to develop an exposure index, using solvent consumption rates, ventilation and respirator usage.[13,14] Other studies

were able to create exposure indices from a variety of sources including job titles and limited measured exposure data,[6,8,10,17,21,24,30] although throughout there appears to have been a lack of consistency both within and between studies. The lack of valid, consistent, quantitative or semi-quantitative exposure indices is a major deficiency in these studies. Effects have been attributed to solvent exposure primarily based on differences between exposed and nonexposed control groups, rather than based on the presence of a demonstrated dose-effect relationship.

2.1.1 Auditory Studies

Brainstem auditory evoked potentials (BAEP) are used to assess the integrity of the auditory pathway from the eighth nerve to the auditory cortex and, thus, auditory dysfunction.[31,32] Results of these studies with respect to solvent exposures have been equivocal. Neurophysiological testing, including BAEPs, of 48 long-term paint solvent exposed workers, with no clinical symptoms, compared with 40 nonexposed controls yielded inconclusive results.[10] The authors found no exposure-effect relationships and attributed the inconclusive results to an insufficient number of subjects. Altmann *et al* failed to demonstrate BAEP differences between volunteers exposed to 50 parts per million (ppm) perchloroethylene and those exposed to 10 ppm.[25] A neurological investigation of hexane exposed press proofing workers in Taipei, using evoked potentials, including BAEP, demonstrated chronic toxic effects.[22]

In a group of 11 subjects, exposed to a variety of mixed solvents, Ödkvist *et al* conducted a series of audiological tests.[28] Taking into account age and noise exposures, pure tone audiometry was normal. Cortical response audiometry and interrupted speech discrimination were more frequently abnormal in the exposed subjects, compared with a nonexposed control group. Subsequently, the study was expanded to include more subjects and further tests, with essentially similar results.[33] Interestingly, the prevalence of abnormal results was highest for those with a confirmed diagnosis of solvent induced psycho-organic syndrome (POS) and lowest for a group exposed to jet fuel. Möller *et al* conducted a battery of audiological and otoneurological tests on 9 subjects with a confirmed diagnosis of solvent induced POS and on 9 nonexposed controls.[29] Pure tone audiometry was normal, although for several of the audiological tests the POS subjects had significantly higher prevalences of abnormalities.

2.2 Effects of Chronic Solvent Vapour Abuse (Glue Sniffing)

In addition to occupational exposures, there are reports in the literature describing adverse effects associated with chronic solvent vapour addictive abuse, often paint or glue sniffing. The reported major component of the solvents associated with abuse is toluene. The level of exposure, a consequence of the purity of the solvent, concentration of the vapour, duration of the exposures and frequency of abuse, is generally unknown, although presumed to be of short duration and extremely high

concentrations. Chronic abusive inhalation of spray paint or glue has been reported to cause a broad range of acute and chronic central nervous system symptoms,[34] including muscle weakness, gastrointestinal complaints, peripheral neuropathy,[36] cerebellar degeneration[36,37,38] and permanent encephalopathy.[39,40]

Hormes *et al* conducted a study of 20 subjects (mean age 27, range 18 to 37) with a history (greater than 2 years, mean duration 12 years) of chronic solvent vapour abuse. Following a minimum of 1 month abstinence (mean duration of abstinence 10.7 months) a consistent pattern of neurological abnormalities was found, including cognitive impairment, but no peripheral neuropathy. Interestingly, two of the 20 subjects were found to have a sensorineural hearing loss and three had abnormal BAEPs.[41]

A case of a 27 year old chronic glue sniffer who exhibited not only the typical central nervous system symptoms, but also two additional deficits, progressive visual and hearing loss, has also been described.[42] The bilateral sensorineural hearing loss occurred rapidly, and the audiogram pattern was described as relatively flat, with a slight increase in hearing loss in the higher frequency range. In addition, abnormal brainstem auditory evoked potentials have been described in two chronic paint sniffers, also displaying cerebellar dysfunction, optic neuropathy and dementia.[43]

These latter three reports suggest the possibility that certain organic solvents may

display ototoxicity. However, it is important to recognize the limitations associated with these studies. The number of subjects was small, either individual case reports or, in the case of the study by Hormes,[41] only 20 subjects of whom 2 showed hearing loss. Further, the nature of the exposures received by solvent abusers is different from that expected in an occupational or environmental setting. The abuser receives extremely high, rather short duration exposures, capable of causing an essentially immediate acute response (the 'high'). The frequency of abuse, thus the frequency of these extremely high peak exposures, varies with the individual. Chronic occupational exposure occurs at much lower levels, but the duration is much greater, typically a full workshift, five days a week, over many years. Clearly the chronic and acute effects may substantially differ due to these variations in exposure profile.

2.3 Styrene-Specific Effects

Styrene ($C_6H_5CH=CH_2$), a colourless, oily solvent, with an odour threshold of 0.1 ppm, is an irritant of the skin, eyes and mucous membranes.[44] A variety of potentially adverse effects have been investigated. Since its chemical structure is similar to benzene, a number of studies have examined the possibility of an association between styrene exposure and excess incidence of leukemia and lymphoma. In a mortality survey of 2,904 employees working in the development or manufacture of styrene-based products, Ott *et al* found an increased incidence of lymphatic leukemia among a subgroup of workers who had exposure to polymer extrusion fumes, solvents and colourants.[45] However, he was unable to establish a

dose - response relationship. Recently, Bond *et al* completed an 11 year update of mortality experience of the same cohort and found that the mortality from leukemia was slightly less than expected, in contrast to the initial study.[46] Hodgson *et al* examined the mortality of 622 workers with a minimum of 1 year history of employment in a styrene plant.[47] A statistically significant excess of lymphoma deaths was found in the exposed population, although, as in the study of Ott[45], no correlation with duration or level of exposure could be found. Several additional investigations of mortality patterns of styrene exposed workers have failed to demonstrate excess incidence rates of leukemia or lymphoma.[48-51] Stengel *et al* have reviewed the evidence for association of styrene exposure and cancers of the haematopoietic tissues and have suggested that low styrene exposures and concomitant exposures to other agents (such as benzene) introduced major weaknesses in many of these studies.[52] They have also emphasized that the ability to detect long latency cancers in these studies was limited. A significant relationship between styrene exposure and certain haematological parameters, such as mean corpuscular haemoglobin concentration and mean corpuscular volume, was however shown.

Interestingly, Coggon and colleagues[49] found a slight, though not significant, increase in lung cancer in workers manufacturing glass-reinforced plastics products. More recently, Wong[51] also found an increase in respiratory cancer in workers from the reinforced plastics and composites industry. Although styrene exposure was not associated with the increase, a significant association was demonstrated between

cigarette smoking and respiratory cancer. Thus, at present, there appears to be little firm evidence of an association between styrene exposure and leukemia, lymphoma or other cancers.

Conflicting reports exist of an association between exposure to styrene and abnormal reproductive outcome. Lemasters *et al* have shown a 4% reduction in birth weights for women working at the most highly exposed jobs, such as laminating, rolling or spraying, at fibreglass boat manufacturing plants. This reduction was not, however, statistically significant ($p=0.08$).[53] No dose - response trend was seen. Exposure to organic solvents (not specifically styrene) during the first trimester has been shown to be significantly associated with spontaneous abortion.[54,55]

2.3.1 Acute Neurological Effects of Styrene

In an early study of acute neurological effects of styrene exposure, Stewart *et al* exposed human volunteers to 50, 100, 200 and 375 ppm for periods of one to seven hours.[56] At 375 ppm (1600 milligrams per cubic meter, mg/m^3) for one hour, the majority of subjects experienced nausea and headaches, as well as objective signs of neurological function impairment. Ödkvist et al also exposed healthy volunteer subjects to 87 to 139 ppm styrene in a series of experiments examining vestibulo-oculomotor disturbances.[57] Styrene exposure induced abnormal results in several of the tests used.

Cherry *et al* assessed acute behavioural effects by comparing pre- and post-shift performances for styrene exposed workers and for nonexposed controls.[58] Although both control and exposed workers experienced mood changes over the shift, this was greater for the exposed group and was correlated with blood styrene concentrations. Reaction time improvements over the shift occurred only for nonexposed and low exposure subjects; those with high exposure to styrene had unchanged reaction times. However, no differences were observed between the two groups in other objective measures of performance. Based on questionnaire data, exposed subjects reported more fatigue than did controls. In a subsequent study, Cherry *et al* confirmed the findings with respect to mood changes and reaction times, for styrene exposed workers.[59]

Edling and Ekberg examined 12 men exposed to low levels of styrene (below 110 mg/m^3 - 25 ppm) and 10 nonexposed control subjects.[60] No differences were observed in either simple reaction time tests or in reported symptoms, suggesting that no acute effects occur at such low levels.

2.3.2 Chronic Neurological Effects of Styrene

A series of early studies was carried out on a group of 98 male hand laminators, occupationally exposed to styrene in the manufacture of reinforced polyester plastic products. The styrene exposed group had significantly greater

visuomotor inaccuracy and poorer psychomotor performances than 43 nonexposed concrete reinforcement workers.[61] In addition, variables measuring visuomotor speed and memory were related to duration of exposure. Thus, a dose-effect relationship was demonstrated. Using the same study group, electroencephalographic (EEG) abnormalities were more prevalent in the styrene exposed group than in the control group or the 'normal' population.[62]

In a clinical field examination of 494 workers of a styrene monomer manufacturing and polystyrene polymerization plant, 13 percent experienced prenarcotic symptoms of dizziness, headache, nausea and incoordination, with a significantly more frequent occurrence for those in the higher styrene exposed group.[63] In addition, abnormalities in nerve conduction velocities were found.

Similarly, Rosén *et al* demonstrated that 10 workers with styrene exposures clearly above the threshold limit value (50 ppm) had signs of mild sensory neuropathy, similar to that found in workers heavily exposed to organic solvents.[64] Styrene exposure was suggested as having a contributory role. Some changes in EEG's were also attributed to styrene exposure.

Neurophysiological examinations, using nerve conduction velocities, were

conducted on 11 styrene exposed workers and compared with those of 11 age-matched controls.[65] No significant differences were found between the two groups, nor were apparent dose-effect relationships observed, confirming a similar finding by Seppäläinen and colleagues.[62] Conversely, Cherry and Gautrin were able to demonstrate styrene exposure dependent, modest sensory nerve conduction deficits in workers in Canadian fibreglass manufacturing plants.[66] Murata *et al* also found significantly reduced nerve conduction velocities in 11 styrene exposed workers, compared with unexposed controls.[67] Reaction time changes, similar to those found by Cherry *et al* in acutely exposed individuals,[58] were also observed by Cherry and Gautrin in the 50 chronically exposed Canadian fibreglass reinforced plastics manufacturing workers.[66]

Mutti *et al* administered various neuropsychological tests to 50 styrene exposed workers and 50 sex-, intelligence- and age-matched controls.[68] Styrene exposure was gauged, using total urinary styrene metabolites, measured once, just prior to the testing. Significant exposure-response or -effect relationships were found, confirming the effects on visuomotor ability, visuoperceptive accuracy and reaction times found by Cherry[58,59] and Lindström.[61] Mutti *et al* suggest that their more definitive findings were likely related to the longer duration of exposure in their study group, as well as to the intelligence matching in the design.[68]

Otoneurological tests were administered to 18 workers who had long term exposure to styrene at levels below 25 ppm (110 mg/m^3) and compared with the results from a reference group.[69] The tests revealed significant disturbances in some components of the central equilibrium and auditory systems. Pure tone audiometry and speech discrimination scores were not remarkably different when age and noise exposures were considered, indicating normal cochlear function. However, 7 of the 18 exposed workers displayed abnormal results in 'distorted speech' and/or in 'cortical response audiometry' tests, suggesting possible central auditory pathway disturbances.

Styrene exposure has also been shown to induce an early appearance of a dose-dependent colour vision loss.[70]

2.4 Animal Studies

Pryor and co-workers have conducted a series of experiments on rats, investigating neurobehavioural effects of exposures to a series of aromatic hydrocarbons.[71-77] Using a multisensory conditioned avoidance response (CAR) task and a tone intensity discrimination task, it was shown that weanling rats exposed to toluene (900 or 1400 ppm, 14 hours per day, 7 days per week, 14 weeks) by inhalation showed learning deficiencies, when tested within hours after the exposure had ended.[71] In a subsequent study when rats were tested 3 days after exposure, learning responses to the CAR task were found to be normal, suggesting that the cognitive deficits in the

earlier study were related to acute, rather than chronic, effects of toluene.[72] In addition, Pryor *et al* showed that in rats exposed to either 1400 or 1200 ppm toluene (14 hours per day, 7 days per week for 5 weeks) hearing was unimpaired at a frequency of 4 kHz, slightly impaired at 8 kHz and markedly impaired at 12 kHz and above.[72] This permanent, toluene-induced, high frequency sensorineural hearing loss was confirmed using brainstem auditory evoked responses tested 2.5 months after the termination of the exposures.[73] In a later study it was noted that young, prepubertal rats were more severely affected than older rats.[74] Subsequently, a series of experiments were conducted to define toluene concentration and inhalation exposure patterns which result in ototoxicity, above 8 kHz, in rats.[75] Ototoxic effects were also demonstrated when the toluene was administered not by inhalation, but by subcutaneous injection.[76]

Similar studies were carried out in rats exposed to inhalation of mixed xylenes and styrene. Both xylene and styrene caused marked hearing loss as assessed by behavioural and electrophysiological test methods and both solvents appeared to have a more potent ototoxic effect than did toluene.[77] Exposure to 800 ppm styrene for three weeks, 14 hours per day, or 800 ppm xylene for 6 weeks caused definite evidence of ototoxicity, whereas exposures to 700 ppm toluene for 15 weeks had been demonstrated earlier[75] not to cause hearing loss. Further, xylene and styrene induced ototoxicity even at frequencies as low as 2 kHz.

Expanding further on the work of Pryor and colleagues, Sullivan *et al* evaluated both morphological changes, hair cell changes of the Organ of Corti, and functional changes, as evidenced by BAER thresholds, in rats exposed orally to toluene.[78] All toluene treated rats were found to have a loss of outer hair cells in the middle and basal turns of the Organ of Corti. A correlation ($r=0.74$) was found between increasing loss of outer hair cells and increasing BAER thresholds in the 2 to 8 kHz frequency range. This study demonstrated that the auditory changes that have been identified were likely causally related to cochlear hair cell loss.

The interaction between exposure to noise and toluene on auditory function in rats has also been studied, using BAER thresholds.[79] On exposure to toluene alone, a statistically significant hearing loss was observed compared with nonexposed controls, particularly at 6.3 and 12.5 kHz. Some improvement was noted in the auditory thresholds one month after exposure and again a similar trend 6 months later. Exposure to noise alone also resulted in a measured hearing loss compared with controls; but the losses above 6.3 kHz were of greater magnitude than those associated with only toluene exposure. Interestingly, rats exposed first to toluene followed by noise, demonstrated a hearing loss which was greater in magnitude than the sum of the loss found for rats exposed to toluene alone and noise alone, suggesting that noise can potentiate the effect of previous toluene exposure. In a later study, Johnson *et al* demonstrated that exposure to noise, followed by toluene, resulted in an auditory impairment greater than that found for either exposure alone; but not greater than the

sum of these individual losses.[89] This demonstrates that the sequence of exposure may affect the degree of auditory impairment observed.

There are several well known limitations to the extrapolation of results from animal species to humans. Species differ in metabolism, absorption, excretion, storage and other physiological effects and thus inferences from an animal model to the human condition must be made with caution. All of the above described studies used the rat and their consistent findings leave little doubt that certain solvents have an ototoxic effect in the rat. Another limitation of animal studies is the problem associated with dose. Toxicologic effects are generally dose-dependent. In all of the above studies, the animals were exposed to unrealistically high levels for different time schedules than those to which humans are likely to be exposed under occupational situations. This seriously limits extrapolation of the results of animal studies to people in the workplace.

2.5 Hearing Loss

Hearing loss can generally be categorized as being conductive or sensorineural. ***Conductive*** hearing loss occurs when an abnormality or malfunction of the outer and middle ear systems decreases the amount of sound energy reaching the inner ear. It can be associated with excessive ear wax, a ruptured or heavily scarred ear drum, fluid in the middle ear (otitis media), dislocated or missing elements of the ossicular chain or otosclerosis. Conductive hearing losses are typically reversible, through

either surgical or medical interventions.[81,82] *Sensorineural* hearing losses are characterized by irreversible damage to the inner ear and/or the higher nerve centres of the auditory system. The deficits in hearing associated with aging, noise exposure, hereditary factors, diseases, such as mumps, ototoxic drugs and chemicals, head injuries and barometric pressure changes are all sensorineural in type.[81] The effects of age and industrial noise exposure have been extensively studied and well documented. Differences in hearing loss have also been ascribed to sex and race. Other potentially contributing factors such as blood pressure, smoking, certain drugs and chemicals have also been investigated.

2.5.1 Age and Noise Exposure

The progressive loss of hearing acuity, which occurs primarily in the upper frequencies, associated with advancing age has been called *presbycusis* and has been demonstrated and described by many investigators.[83-89] Robinson and Sutter[83] analyzed numerical data on hearing threshold levels as a function of age, obtained from the literature, and derived a formula for predicting the effect of age on hearing thresholds, for populations screened for otological disease and noise exposures. Using these formulae, Table 2-1 provides an example of the expected hearing loss, as decibels hearing level (dBHL) at 4 kHz for men (♂) and women (♀) with increased age, demonstrating the association between hearing loss and age.

Table 2-2 illustrates the frequency dependent nature of the age-related deficit in hearing, demonstrating the more marked effect at high frequencies. This is graphically illustrated in Figure 2-1 (page 35).

Table 2-1: Expected Hearing Loss at 4 kHz by age (dBHL)						
HEARING LOSS	30 years		50 years		70 years	
	♂	♀	♂	♀	♂	♀
Median	2.3	1.3	16.4	9.2	43.3	24.3
Upper Quartile	8.6	6.9	26.9	17.2	61.9	36.9
Lower Quartile	-2.7	-3.2	8.0	2.8	28.4	17.9

adapted from: Robinson and Sutter[83]

Table 2-2: Expected Hearing Loss (dBHL) by Frequency (♂, age=50yr)				
HEARING LOSS	FREQUENCY			
	2 kHz	4 kHz	8 kHz	12 kHz
Median	7.2	16.4	22.5	36.9
Upper Quartile	14.2	26.9	36.4	56.9
Lower Quartile	1.5	8.0	11.4	20.8

adapted from: Robinson and Sutter[83]

Similarly, Royster *et al* developed expected hearing threshold levels for white men and women using a statistical smoothing technique.[84] For a 50 year old white male, the expected hearing loss is given as 14.2 dBHL at 2 kHz, 32.2 dBHL at 4 kHz and 39.0 dBHL at 6 kHz. These values, at 4 and 6 kHz, are higher than those reported by Robinson and Sutter.[83] This difference may be

a result of the inclusion, by Royster, of hearing loss caused by noise of a non-occupational nature together with the age related loss.

Although the existence of the relationship between hearing loss and aging has been demonstrated convincingly and conclusively, very little is understood about the precise nature of the effect of the aging process on hearing. Hinchcliffe has reviewed briefly the suggested possible mechanisms including mechanical factors, sensorineural, circulatory or biochemical mechanisms.[88]

There are clearly differences in hearing loss patterns between men and women, with the former having greater hearing loss as illustrated in Table 2-1 and also demonstrated in several other studies.[83-85,87,90] Robinson[85] has suggested that differences between age-related hearing loss in men and women become very marked with increasing age, and more so in randomly selected populations than in screened populations.

The adverse effect of exposure to noise on hearing has been the subject of extensive study in the past decades. Seminal investigations to establish a quantitative relationship between industrial noise exposure and the resultant loss of hearing acuity were conducted, in 1963-68, by Burns and Robinson.[91] The hearing acuity and noise exposures of over 750 subjects, exposed daily to essentially continuous noise for up to 50 years were examined. From the data,

a method for predicting the hearing deficit expected from a given noise exposure was developed. Burns and Robinson, recognizing that the effect on hearing is a combined function of noise intensity and exposure duration, developed the concept of *Noise Immission Level*, noise level in decibels plus 10 times the logarithm of a duration (years), which has been an important concept in many epidemiological studies of noise effects on hearing. Interestingly, women were found to be more resistant to noise damage than were men.

The auditory effects of noise have been reviewed by Kryter[92] and Ward[81,93] Brief exposures to high noise levels can cause a temporary reduction in hearing acuity or temporary threshold shift (TTS), which progressively improves with increasing rest time, as the ear recovers from the 'overstimulation'. Excessive and prolonged exposure to noise can result in a permanent loss of hearing, or permanent threshold shift (PTS). The most distinctive features of this noise-induced hearing loss (NIHL) are that it is insidious, initially affecting hearing thresholds at 4 kHz and spreading to other frequencies and becoming more pronounced as it advances. Early NIHL therefore, is characterized by the *4 kHz dip or notch*, a marked reduction in acuity at 4 kHz, with improved hearing to 8 kHz. (Figure 2-2, page 36) In addition, the non auditory effects of sound, although beyond the scope of this investigation, have been reviewed by Borg, including potential effects on the cardiovascular, endocrine and

somatomotor systems, the sensory functions and the ability to fall asleep.[94]

Age-related hearing loss accrues concurrently with the adverse effects of noise exposure and, consequently, greatly affects the estimates of risk of hearing impairment associated with a particular noise exposure. Although the mechanisms are not fully understood, the concurrent effects of age and noise on hearing loss are well established, such that an international standard exists (ISO 1999:1990).[95] This provides procedures for estimating the hearing impairment due to noise exposure of populations free from auditory impairment other than that due to noise, with allowance for the effects of age, or of unscreened populations whose hearing capability has been measured or estimated. Using this standard procedure, the expected hearing loss for a population of 50 year old males, exposed, on a daily basis, to 90 dB(A) for 25 years can be compared to that expected for the same population given an exposure of 100 dB(A) also for 25 years. (Table 2-3) The first row of Table 2-3 provides the expected hearing loss due to age alone. These values are similar to those in Table 2-2, since the work of Robinson and Sutter[83] was heavily used by ISO. The remainder of the table provides the expected age-corrected NIHL and the total hearing loss, combining both age and noise effects, at exposures of both 90 and 100 dB(A). The median, upper and lower quartiles of hearing loss, shown on all three tables, emphasize the great variability associated with hearing losses due to both age and noise exposures.

Table 2-3: Expected Hearing Loss for 50 yr old men with noise exposures

	FREQUENCY					
	2 kHz			4 kHz		
	1/4[1]	MED[1]	3/4[1]	1/4	MED	3/4
AGE CONTRIBUTION	1.6	7.2	14.2	8.2	16.4	26.9
Exposure: 90 dBA, 25 yrs						
NIHL corr'd age[2]	3.6	4.4	5.8	10.7	11.6	12.5
TOTAL HL[3]	5.2	11.6	20.0	18.9	28.0	39.4
Exposure: 100 dBA, 25 yrs						
NIHL corr'd age[2]	14.4	17.8	23.4	29.7	32.4	34.8
TOTAL HL[3]	16.0	25.0	37.6	37.9	48.8	61.7

1 - Lower quartile, median and upper quartile
2 - NIHL Corrected for age contribution
3 - Sum of Age Contribution and NIHL

- adapted from: ISO 1999[95]

It is difficult to isolate the relative contributions of age, industrial noise exposure and non-occupational noise exposure to hearing loss. The development of expected hearing loss data, such as the ISO standard, permits a comparison between groups exposed at a particular noise level, and a 'nonexposed' group, of the same age and sex. Difficulty arises with the selection of the nonexposed group. This can be a highly screened, otologically normal group; or, an unscreened, randomly selected group from a population. Robinson provides evidence that the use of an unscreened group is more appropriate, since it takes into account non-occupational noise exposures.[85]

Recently, in an 8 year study to obtain longitudinal hearing threshold data, median hearing thresholds were found to be almost identical[96] to the age and sex-matched unscreened population data of Robinson.[85] Similarly, a noise nonexposed control group identified by Lutman *et al* was also found to be inconsistent with the highly screened data.[87]

It has been shown that there is an asymmetry between the hearing threshold levels of the left and right ears. In a series of studies, Pirilä and colleagues demonstrated that the left ear was, on average, significantly worse than the right ear among both male and female subjects.[97-99] Exposure to gunfire could not explain these differences,[97] nor could handedness.[98] The authors suggested that the inferiority of the left ear, particularly at 4 kHz, was likely associated with noise damage.[96]

2.5.2 Other Factors

A series of recent studies used multivariate analysis to identify importa.it factors affecting hearing loss. Age, noise exposure and sex were identified by all as the most important factors. Socioeconomic background,[87] vibration exposure as vibration-induced white finger disease or Raynaud's Syndrome,[86,90] elevated LDL-cholesterol,[86] use of antihypertensive agents,[86] and elevated diastolic blood pressure[90] have been found to be significant factors. In these studies, smoking did not appear to contribute

significantly[86,90] nor did systolic blood pressure.[86,90] Head injury and ear disorders were found to be unimportant, compared with age, sex and noise exposures.[100]

Touma has reviewed the evidence for metabolic factors having an effect on hearing loss, and has suggested that hyperlipoproteinaemia and atherogenic diets increase the susceptibility of the cochlea to loud noises, especially at high frequencies.[101]

In a study of 85 workers with long term exposure to noise in excess of 85 dB(A), and 85 noise nonexposed workers, both systolic and diastolic blood pressure (BP) were significantly elevated in the noise exposed group, suggesting the possibility that noise exposure leads to elevated BP.[102] In a larger study, industrial noise exposure was found to be associated with higher ambulatory BP and heart rates, in men under 45 years of age, with the effect on BP diminishing considerably with age.[103] Conversely, Talbot *et al* demonstrated in men over 63 years of age a marginally significant increased prevalence of high BP (or taking BP medication) among those with severe NIHL.[104] On the basis of a review of the relevant literature, Touma has suggested that hypertension and heart disease increase the susceptibility of the cochlea to noise, increasing the risk of NIHL.[101]

In contrast to the aforementioned studies,[86,90] a study of 2,348 noise exposed white males showed that smokers were at an increased risk of a noise induced hearing loss.[105] In a retrospective analysis of over 600 subjects, smoking quantity and duration was significantly higher for those with impaired hearing, compared with the normal hearing group.[106] This may be due to aromatic hydrocarbons in the smoke, although this is highly speculative. It has also been suggested that cigarette smoking affects blood and plasma viscosity in men[107] and that high frequency hearing impairment is related to plasma viscosity.[108]

2.5.3 Drug Ototoxicity

A number of therapeutic agents have been found to be ototoxic, that is, to cause functional impairment and cellular degeneration of the tissues of the inner ear, resulting in a hearing loss. Agents such as aminoglycoside antibiotics, such as streptomycin, neomycin and kanamycin,[109-111] salicylates,[112,113] diuretics[114] and chemotherapeutic agents, specifically cis-platinum[115-119] have been studied extensively. The aminoglycosides cause permanent hearing loss, affecting initially the higher frequencies, spreading to the lower frequencies with continued intake of the drug. Cis-platinum related hearing loss occurs at the higher frequencies, generally over 6 kHz. Diuretics can cause a significant hearing loss at 1 kHz and above, following administration, with essentially complete recovery within 24 to 72 hours. The

hearing loss associated with salicylates occurs equally across all frequencies and is a temporary consequence.

The combined effects of these therapeutic agents and noise exposure has also been extensively studied. There appears to be a synergistic interaction between noise exposure and both aminoglycoside antibiotics[120-125] and cis-platinum.[126,127] There is no evidence that combined exposures to salicylates or diuretics and noise result in any potentiation effect.[128,129]

2.5.4 Styrene Ototoxicity

Very few studies have been conducted examining specifically the effect of solvent exposure, or the effects of simultaneous solvent and noise exposures, on hearing acuity in humans. Barregård and Axelsson[130] cited two early studies in Eastern Europe which demonstrated increased incidence of sensorineural hearing loss associated with carbon disulphide and trichloroethylene exposure, as well as a Mexican study which attributed sensorineural hearing loss to n-butanol exposure. Barregård *et al* described 4 case reports of painters who presented with hearing losses that were much more pronounced than would have been expected based on their noise exposures. An ototraumatic interaction between noise and solvents was postulated.[130] A possible relationship between exposure to industrial solvents and hearing loss was also suggested by Bergström *et al*, after finding an

unexpectedly high proportion of hearing losses in workers exposed to solvents and relatively low noise levels, compared with noise exposed, solvent nonexposed workers.[131] In workers exposed to both noise [86-89 dB(A)] and carbon disulphide (90 mg/m^3), the percentage displaying a hearing loss was much higher than expected based on the noise exposure, causing the authors to postulate a connection between the two agents.[132]

One study in the Netherlands by Muijser *et al*[2] examined the effects of occupational exposure to styrene on high frequency hearing thresholds. In this study, hearing thresholds were evaluated at frequencies up to 16 kHz in workers exposed to styrene in a glass fibre, reinforced plastic products manufacturing environment and compared with those of a control group of styrene nonexposed workers. As expected, age was found to have a significant influence on hearing thresholds across both the high frequency range as well as the conventional audiometric range. Therefore, multiple regression analysis was used to control for the effects of age. The means of the hearing thresholds in the control workers were higher than for the exposed workers in the high frequency ranges, although these differences were not statistically significant. No significant differences were noted between the hearing thresholds of control workers and those of the 'directly' exposed styrene workers. However, a statistically significant difference was noted in the hearing thresholds between the directly exposed styrene workers and the

indirectly exposed styrene workers. This relates to a comparison of high exposures (138 mg/m^3) versus lower exposures (61 mg/m^3). Interestingly, the differences in hearing thresholds between these two groups were most prominent at 8 kHz frequency range. This study suggests that the ototoxic effect of styrene observed in rats occurs also in humans, at styrene exposure levels below the current Threshold Limit Value of American Conference of Governmental Industrial Hygienists of 213 mg/m^3 (50 ppm).[133] However, the study design, as well as the execution, were flawed in several aspects, thereby compromising the findings.

In any study seeking to investigate the potential ototoxic effects of chemicals it is clearly imperative to control for the most significant ototoxic workplace hazard known, namely, industrial noise exposure. In the aforementioned study, noise exposures were not determined for each subject, although some instantaneous sound level measurements were taken in the two plants. However, the data collected showed that the noise levels in the control plant were in the order of 10 dB(A) higher than in the styrene plant. This alone could be sufficient to obviate any subtle effects of styrene on threshold shift. Furthermore, the authors described, based on purely subjective impressions, that the frequency spectrum of the noise in the control plant was "quite different" from the noise in the styrene exposure plant. Thus, the choice of control group was probably inappropriate.

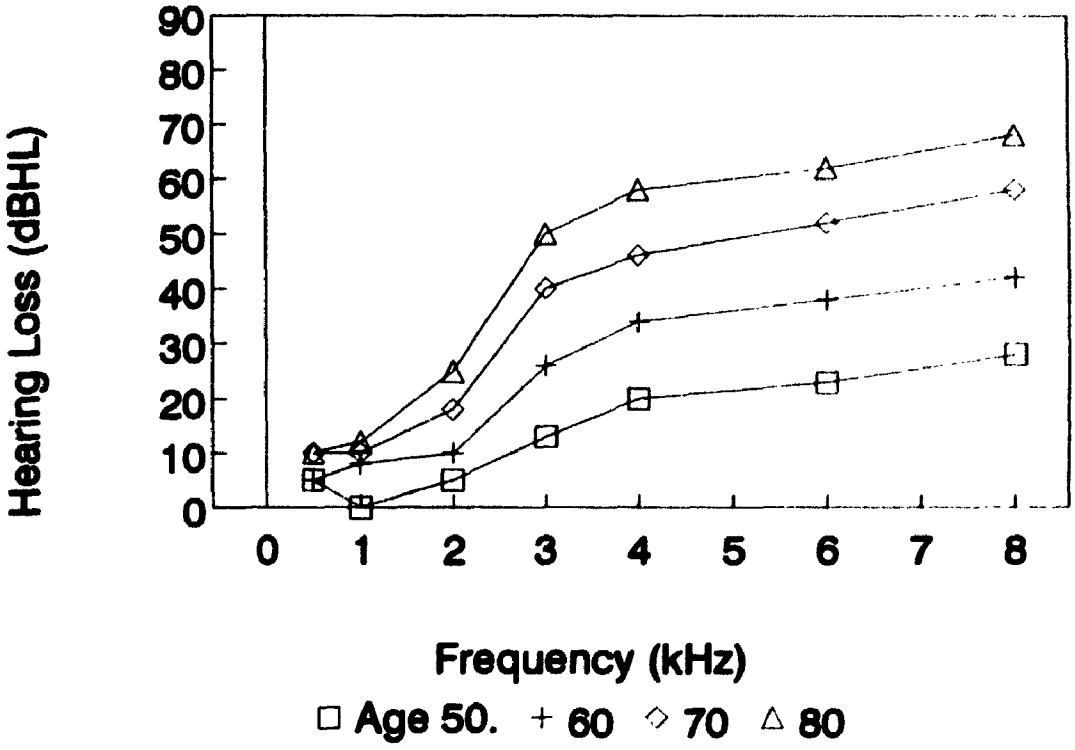
In addition to problems with the control group, there were several other serious deficiencies in this study. The authors appeared to assume that the current level of exposure to styrene, as measured over the three day sampling period, would be indicative of long-term exposure. It might have been more informative to consider exposure categories on the basis of both current exposure level as well as duration of employment in that particular area. Naturally, any historical exposure data would be useful in determining a valid exposure index. In addition, other potential contributing factors such as smoking and therapeutic drug usage should have been examined.

2.6 Summary

The information available to date regarding the ototoxic potential of aromatic hydrocarbons, particularly styrene, toluene and xylene, although highly suggestive, is certainly far from definitive. Neurophysiological and neurobehavioural research suggest the existence of a biological basis for such ototoxicity. Abnormal brainstem auditory evoked responses in some studies indicated auditory dysfunction. Descriptive studies documenting hearing loss and other neurological disorders associated with chronic paint or glue sniffing provide further evidence for a causal relationship. However, a great difference exists in exposure patterns between chronic abusers of paints and glues and exposure patterns in industrial workplaces. The reproducible studies on the rat, with some evidence of an exposure-response relationship, are highly suggestive, particularly for toluene, xylene and styrene. The demonstration of a

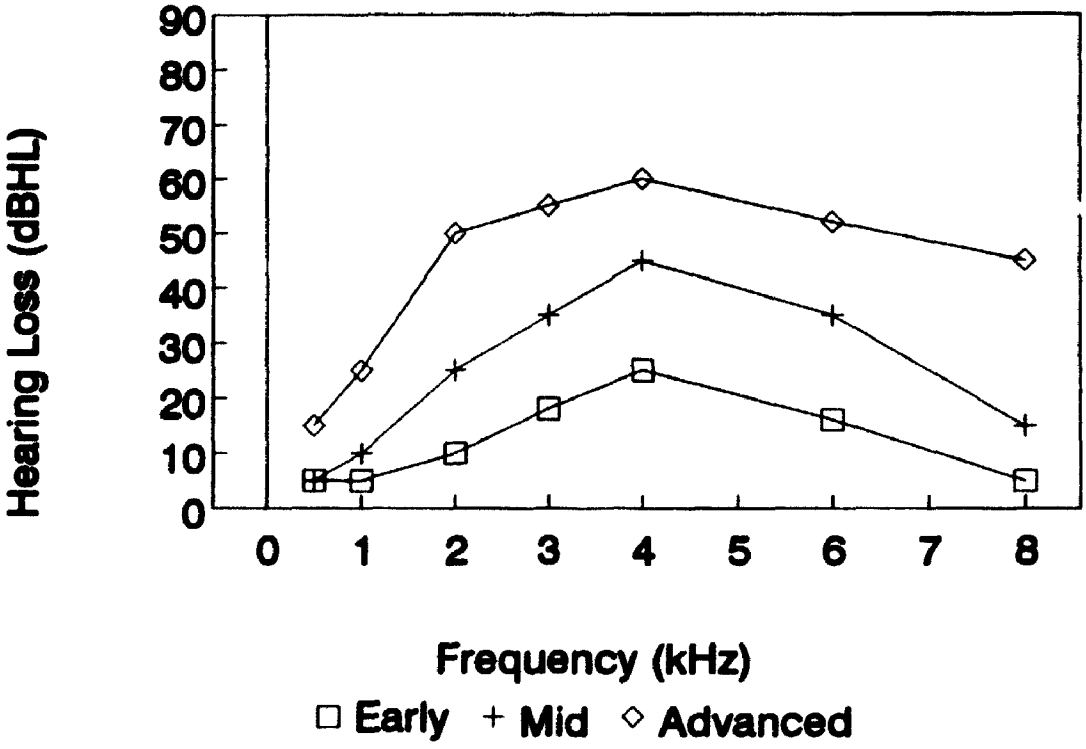
synergistic effect between toluene exposure followed by noise exposure provides further evidence. Nevertheless, there are significant limitations in applying the results of animal studies to humans. Ototoxic therapeutic agents provide a useful analogy and the existence of a synergistic relationship between certain ototoxic drugs and noise exposures strongly favours a chemical plus noise interactive model. The studies which suggest a direct link between solvent exposure and hearing loss are few, and not entirely convincing. The recent study by Muijser,[2] while flawed, does raise the serious possibility that occupational styrene exposure at levels currently below acceptable standards,[133] may have an ototoxic effect.

Figure 2–1: Typical Audiogram Pattern for Presbycusis



adapted from Sataloff and Michael (82)

Figure 2–2: Typical Audiogram Patterns for Advancing NIHL



adapted from Sataloff and Michael (82)

CHAPTER 3: MATERIALS AND METHODS

3.1 Study Design

The initial design proposed for this study was a 2 x 2 factorial design, the two binary factors being the absence or presence of styrene and noise exposure, and the principal outcome variable of interest being hearing loss. The styrene factor was defined literally, with the absence meaning no styrene exposure. The noise factor was defined such that exposures less than 80 dB(A) were considered *no noise* exposures. Sixty-five workers were to be selected from each of the four exposure groups: styrene and noise exposed (S,N), styrene exposure with no significant noise exposure (S,n), no styrene exposure but with noise exposure (s,N), and no styrene no noise exposure (s,n). Because hearing loss is related to age and possibly related to duration of employment, both of these variables were to be used as sampling strata within the design. For the purposes of sampling, the age variable was categorized into three levels: less than 35, 35 to 45 and 46 to 56 years and the duration of employment variable into the three groups: less than 2, 2 to 10 and over 10 years. Because hearing loss may differ between men and women[92,93] and the former comprise the majority of workers in the styrene industry, only male workers were included in this study.

During the initial phases of study preparation it became evident that a full 2 x 2 factorial design would not be possible due to the limited number of plants available, making it impossible to recruit the necessary number of subjects for each of the strata within the four exposure groups. Consequently, all available male workers from each

plant were asked to participate, including assembly and other non directly exposed workers, including warehouse, shipping and receiving, engineering and office workers, in order to include workers exposed to a wide range of styrene and noise levels.

Each participant completed a questionnaire, administered by interview, which provided information on demographic characteristics, smoking history, occupational history with specific reference to solvent and noise exposures, use of personal protective equipment, particularly for hearing and breathing, recreational exposures to noise or solvents, and family or personal history of hearing loss or injury. Audiometry was performed on all workers, at the beginning and again at the end of the work shift, on the same day as the questionnaire was completed. The repeated audiometric measurements allowed for the assessment of the acute effects of exposures over the workday. These repeated, post-shift measurements may be somewhat influenced by a learning effect;[92,134] however, it is expected that the magnitude of any such effect will be similar across all groups and therefore no bias was anticipated.

Full shift personal TWA styrene exposure measurements were taken for each participant, on the same day that the audiometry was performed. While single, full shift styrene exposures can not be taken to represent adequately a working life exposure, these exposure measurements were vital to the assessment of possible acute effects of styrene on hearing loss. Since no precise retrospective exposure data

existed, the current styrene exposure data were also used to construct an exposure index for the assessment of chronic effects for each subject. Average exposures within job categories within each plant were coupled with job classification histories and work durations to construct the exposure index.

Noise exposure measurements were determined for each study participant using personal noise dosimetry. Due to the importance of noise as a potential confounding factor, as well as the ubiquitous nature of noise in the workplace, noise exposures were determined for all participants, except for 7 office workers. The noise exposure data were used in a manner similar to that described for the styrene data.

Typically a worker with noise induced hearing loss suffers, initially, a significant loss in the 4 kHz region ("4K dip") with a recovery at 8 kHz[81,93,101] (Figure 2-2, page 36). Hearing loss due to aging (presbycusis) tends to develop as a general loss across all the higher frequencies (Figure 2-1, page 35). To date it has been suggested that styrene "induced" hearing loss occurs at 8 kHz and above.[2] Therefore, by comparing the patterns of the audiograms, taking into account noise exposure and age in the analysis, it should be possible to differentiate hearing loss associated with noise and age from that associated with styrene exposure. Although full spectrum audiograms were taken on each subject, results from the frequency region of 3 to 8 kHz were emphasized in the analysis of the data.

3.2 Selection of Plants and Subjects

A listing of all plants manufacturing fibreglass reinforced plastic products was obtained from the (1991) Directory of the members of the Society of the Plastics Industry of Canada.[135] Plants in the southern Ontario region, with more than 10 workers, were identified. A total of 26 Ontario plants were contacted. Of these, 12 were no longer in business, were drastically reduced in size to less than 10 plant workers, or had moved the manufacturing facility south of the border. Seven declined to participate on the basis of the telephone discussion and a followup letter, and seven agreed to a site visit by the investigator. During the site visit, the study was described in detail to the plant management, as well as (in most cases) to worker representatives. All of these seven plants agreed to participate in the study. In addition, Nova Scotia Department of Labour inspection personnel contacted 4 large fibreglass reinforced plastics manufacturers and 6 small fibreglass boat builders in Nova Scotia, describing the study and requesting voluntary participation. One of the larger plants immediately declined to participate. The investigator visited the three remaining plants to describe the study. These agreed, as did 4 of the 6 boat builders, to participate. Thus, a total of 14 fibreglass reinforced plastics manufacturing plants were included in the study, as well as one additional office workplace, from which 10 additional noise/styrene nonexposed controls were obtained.

Due to the difficulty in finding additional fibreglass reinforced plastics manufacturing plants, all available subjects from each plant were initially asked to participate, with

the exception of one plant where not all possible workers were approached, since the plant management had agreed to participate in the study for only 6 days. Potential subjects with a history of otologic dysfunction as well as other complicating medical conditions which are believed to be correlated with hearing loss were excluded. For example, workers were excluded from the study if they had a history of draining ears or ear surgery, chronic middle ear infection within the past 3 years, other chronic ear diseases, cardiovascular disorders or hypertension, diabetes, kidney or thyroid disease, or if they were on certain medications such as diuretics or chemotherapeutic agents.[136] Of the 324 subjects initially approached, 9 were excluded for otologic/medical reasons and 16 refused to participate.

3.3 Mobile Field Facility

A 16 foot cube van of plywood and sheet metal construction was rented for the duration of the field component of the study to serve as the field laboratory. An IAC Controlled Acoustical Environment audiometric booth (Industrial Acoustics Co. Inc., Bronx, NY) was mounted inside the van. A small desk and other working surfaces were also installed. The field equipment, packed in convenient protective containers was stored in the van. The van was driven to each plant site and parked in the most convenient location. There were several criteria for the location: easy and quick access for the subjects, as close as possible to a plant entrance; within 75 meters of a power source due to the requirement for 115 volt 15 amp current for the audiometer, lighting and the computer; and, minimal background noise, as far away

as possible from noise sources within the plant, as well as from truck loading docks, forklift operations and train tracks.

At the start of each day, up to 10 subjects were brought, one or two at a time, to the van for the audiometric testing. After this test, before they returned to their workstations, each subject was assigned and given styrene and noise sampling equipment to wear for the full workshift. At the end of the shift, subjects returned to the van, the measuring equipment was removed and the post-shift audiometric testing carried out.

3.4 Consent and Questionnaire

The study and its objectives were described to potential participants, as was the role of each participant. Each participant was informed that the Joint Health and Safety Committee in the plant and plant management would receive only the noise and styrene exposure data for each subject. They, as participants, would receive their personal noise and styrene exposure measurements and their audiometric results. Each participant was asked to sign a consent form (Appendix I). The consent form was signed prior to any further study activity.

The questionnaire, in a computer ready format, was adapted from a number of questionnaires previously used by the investigator. Information including demographic variables, occupational exposure history, with specific reference to solvent and noise,

work practices, use of protective equipment, smoking history, past medical and family history of hearing loss, general hearing complaints and recreational sources of noise or solvent exposures was obtained. In addition, nine questions designed to elicit some general information on self-reported hearing acuity were included. These were excerpted and modified from an extensive hearing measurement scale suggested by Noble and Atherley.[135a] Their inclusion was not related to the primary purpose of this study, but rather to give an indication of their usefulness by comparison with actual hearing acuity data. A copy of the questionnaire is appended (Appendix II). The questionnaire was administered by one of the two field study personnel, trained in the conduct of Occupational and Environmental Health surveys. Questionnaire administration occurred at some convenient time during the day.

3.5 Audiometric Testing

A MAICO Model 26 Automatic Audiometer (Maico Hearing Instruments Inc., Mineapolis, Minesota) was used to obtain hearing loss data. The pre- and post-shift audiometric testing were conducted in the IAC Audiometric Booth, in which the background noise levels met the specifications of the CSA Standard Z107.4-1986 "Pure Tone Air Conduction Audiometers for Hearing Conservation and for Screening" as follows:

Frequency (Hz)	Maximum Ambient Sound Level (dB)
500	21.5
1,000	29.5
2,000	34.5
4,000	42
8,000	45

The two individuals conducting the audiometric testing at the plant sites were fully trained in the approved methods and in the use of the equipment. Each subject was given the same set of instructions regarding the test. This included a brief explanation of the purpose of the testing, which was to determine the quietest sounds one can hear at a series of different frequencies. It was explained that the subject would be presented with a series of three short, rapid tones (beeps) through the headphones and each time these were heard the subject was to press the response button. Subjects were informed that the tones would begin in the left ear and be presented in different pitches. This would then be repeated in the right ear. They were warned that the tones would be extremely quiet, that concentration was necessary and that if they even thought they heard the beeps, a positive response should be made. Once the explanation was complete and the tester was satisfied that the subject understood the directions, the subject was placed inside the booth, glasses and any other obstruction were removed and the earphones carefully mounted. The booth was sealed, the van rear door closed with the tester remaining inside the van and the test begun.

For automatic testing of pure tone air conduction, the MAICO audiometer presents three 0.2 second pulses with a 0.2 second interval between each pulse. The presentation of the three pulses is random in spacing to lessen fraudulent responses. Each tone presentation opens a response period of 2 seconds, during which the subject must press and release the hand held switch for a good response. The automatic program begins with a trial test at 1 kHz for the left ear, with a starting intensity of

40 dB hearing level (dBHL). A negative response or no response at the initial 40 dBHL presentation will result in the audiometer increasing the tone automatically by 20 dBHL. After this, the intensity will increase by 10 dBHL until a positive response or 95 dBHL is reached. After the first positive or good response, the intensity is decreased by 10 dBHL for valid responses and raised 5 dBHL for invalid until a threshold is established. Two positive responses at the same HL tone constitute hearing threshold for that frequency and ear. When the threshold is established at 1 kHz, the audiometer presents 0.5 kHz, establishes a threshold, returns to 1 kHz and retests that frequency. The thresholds of the two 1 kHz tests must be within 5 dBHL of each other for test reliability. If they are not within 5 dBHL the audiometer retests 0.5 and the 1 kHz a third time. If this third test is not within 5 dBHL of the best of the first two, the test is automatically aborted and the tester must provide further clarification to the subject. Once test reliability is established at 1 kHz, the test sequence automatically continues with 2, 3, 4, 6 and 8 kHz for the left ear. If the subject fails to establish a threshold at a given level, after the 1 kHz reliability test, the audiometer skips that frequency and retests once after the normal test procedure is completed. The right ear is then tested in the same manner, including the 1 kHz reliability test. Once the test is complete, the audiogram information is printed. With a few subjects, typically those with some difficulty with the English language, no response was received over the first series (at 1 kHz, left ear) or a series of false positive responses was given. The audiometric testing automatically terminated and the tester conferred with the subject to ensure that the instructions were understood.

In all cases, the testing was completed, although with eight subjects several false starts occurred.

3.6 Styrene Exposure Measurements

Personal time-weighted average (TWA) exposure monitoring was conducted on all subjects, as described above, to determine their exposure to styrene. The conventional integrated sampling method, whereby air containing styrene is drawn at a specified flow rate for a known duration of time through a glass adsorption tube containing 20/40 mesh activated coconut shell charcoal (SKC Inc., Eighty Four, PA), was used. The analytic section of the tube contains 100 mg of the activated charcoal, with the back-up section containing 50 mg. The styrene, as well as other hydrocarbons and volatile organic substances, adsorb onto the charcoal. After sampling, the adsorbed substances are desorbed and quantified based upon the procedure recommended by the National Institute for Occupational Safety and Health (NIOSH, method 1501-aromatic hydrocarbons).[137] Given this determined mass of styrene and the volume of air from which it was adsorbed, a TWA exposure measurement was obtained.

3.6.1 Sampling Method

Five Dupont (P4LC) multiflow and five Dupont low flow (Alpha2) battery operated pumps (EI duPont de Nemours & Co., Wilmington, Delaware) were calibrated prior to the sampling using a portable, conventional soap bubble

flow meter, mini-Buck Calibrator (AP Buck Inc., Orlando, Florida) to provide a known, nominal flow rate of 60 to 70 mL/min through the adsorption tube. Prior to the beginning of the shift, the pumps were allowed to stabilize for a minimum of 30 minutes, then calibrated. The calibration was confirmed immediately after sampling on each day, before the pumps were shut off. The criterion for rejection of the sample was a difference of greater than 5 percent, which never occurred. The actual flow rate was taken as the mean of these two values. The flow rate was selected to maximize collection efficiency and to allow for a full shift sampling period. The pumps were used over two consecutive shifts, then recharged for 12 to 14 hours, overnight.

Each subject was equipped with a numbered charcoal adsorption tube, open at both ends, placed in a protective plastic tube holder, which was clipped to the right collar of the subject and attached to the air sampling pump using Tygon® tubing. For each subject (name and subject ID number), a record was kept of the pump serial number, the charcoal tube number, the time the sampling was begun and the termination time. During the course of the shift, the pump and tube on each subject was examined at least twice to ensure no faults or difficulties. On each sampling day, one tube was opened at both ends, sealed and left in the van, to serve as a blank sample.

The charcoal tube samples, removed from the protective holders and tubing at

the termination of sampling, were securely sealed using the plastic caps provided with the tubes. To prevent desorption or redistribution of the sample, they were stored, on ice, for either immediate transport to the laboratory, if the plant were in the Toronto vicinity, or for transport to a local household type freezer. When sampling was conducted in Nova Scotia, samples were stored for up to 1 week in a standard freezer, then placed in a cooler full of ice packs, and shipped to the University of Toronto, Occupational and Environmental Health Unit Laboratory, by overnight courier. The freezer packs were still frozen when the shipment was received.

3.6.2 Analysis of Charcoal Tube Samples

After storage in the laboratory at -20°C for a maximum duration of 4 weeks, the charcoal tubes were removed from the freezer, the plastic caps unplugged, the glass scored and broken, and the front and back sorbent sections of each sampling tube carefully transferred to separate, labelled 2 mL vials. The glass wool and foam plugs were discarded. One millilitre (mL) of carbon disulphide, CS_2, (99.9% Omnisolv, BDH Chemicals, Toronto, Ontario) was added to each vial which was then tightly sealed with a teflon lined, septum equipped cap. The vials were then placed in a wrist shaker (Burrell Wrist-Action Shaker, Burrell Corp., Pittsburgh, Pennsylvania) for 30 minutes, to allow desorption to occur.

Two gas chromatographs were used in the analysis: A Hewlett Packard Model 5804A (Hewlett Packard Canada Ltd., Mississauga, Ontario) for plants 1,2 and 3; and, a Varian Model 3400, equipped with a Model 8035 Autosampler (Varian Canada Inc., Mississauga, Ontario) for the remainder of the samples. The chromatographic conditions for each are given in Table 3-1 (page 58). The Hewlett Packard instrument is equipped with an HP integrator which measures peak areas. The Varian is operated with the aid of an IBM 80286 (PS2) personal computer and a Varian STAR Integrator software package.

Calibration was done separately for each set of samples run, using five working standards over the range 0.01 to 12.5 mg styrene/mL. The standard solutions were prepared using Styrene (Fisher Certified 99.8%, Monomer Inhibited, Fisher Scientific, Unionville, Ontario) in CS_2. A full set of standards were analyzed prior to each run of samples. During longer runs (greater than 20 samples) two of the standards were re-analyzed in between the samples, as quality control samples. Two standards were analyzed at the end of each run.

Desorption efficiency was determined by the Phase Equilibrium method.[134] The front section of a charcoal tube was transferred to a 2 mL vial and 1 mL of a known styrene standard (as above) in CS_2 was added. The vial was sealed with a teflon lined, septum equipped cap. Three such tubes at each of the 5

levels corresponding to the working standards were prepared in this manner and allowed to equilibrate overnight in a freezer at -20°C. The following day the vials were brought to room temperature and were put on the wrist shaker for 30 minutes. 1 μL of the supernatant was analyzed together with the working standards. The Desorption Efficiency (DE), at each of the 5 concentration levels, was calculated by dividing the average mass (mg) recovered from the CS_2 exposed to the charcoal, by the mass added originally to the solvent. A plot of Desorption Efficiency by mass of analyte recovered was established.(Figure 3-1, page 59)

Regression analysis of the data obtained from the standards was used to ascertain the linearity of the peak areas plotted against the concentrations of analyte over the sample range envisaged. The slope and intercept values obtained from the calibration curve were used to calculate the mass (mg) of analyte in the sample. No detectable levels of analyte were found in the blank samples and therefore blank corrections were unnecessary. The DE corresponding to the mass of analyte found, obtained from the DE curve above, was used to correct for permanent adsorption losses. Thus the mass of styrene in each sample was determined.

3.6.3 Time-Weighted Average Styrene Exposures

The time-weighted average (TWA) exposures to styrene, in mg/m^3, for each

subject were calculated according to:

$$TWA = \frac{\text{mg styrene} \times 1000}{FR \times \text{duration}}$$

where: FR = Flow rate in mL/min
duration = duration of sampling in minutes

3.7 Noise Exposure Measurements

Personal noise dosimeters were worn for one full workshift by each participant in the study. A noise dosimeter is an instrument which performs two functions. The microphone and the instrument itself are placed on a person being monitored, and the microphone is attached on the collar as close to the ear as possible thereby monitoring the "hearing zone". The remainder of the instrument, attached to the worker's belt, automatically computes the desired noise measures. For noise, the equivalent to the TWA exposure for a chemical would be what is known as an *"equivalent sound level"* or L_{eq}, measured in A-weighted decibels. For this study Quest Model M-27 dosimeters (Quest Electronics, Oconomowoc, Wisconsin) were used. The dosimeters provide several types of exposure information: the equivalent continuous sound level (L_{eq}) based on a 3 dB exchange rate; the L_{avg}, based on a 5 dB exchange rate; and percentage dose. The *exchange rate* can be defined as the increase, or decrease, in dB(A) required to give the same noise dose or sound energy for a halving, or doubling, of the exposure duration. For example, a 90 dB(A) exposure for an 8-hour period would be equivalent in terms of dose/energy received, to a four hour exposure of 93 dB(A) using the 3 dB(A) exchange rate; or of 95 dB(A) using the 5 dB(A)

exchange rate. Current Ontario legislation regarding workplace noise exposures specifies the use of the 5 dB exchange rate.[139] However, it has been recognized that the 3 dB exchange rate is scientifically more valid and therefore recently proposed legislation specifies the 3 dB exchange rate.[140] For the purposes of this study the 3 dB exchange rate was used to obtain a noise dose or exposure.

3.8 Data Analysis

All data were entered, by plant, on LOTUS 123 spreadsheets. Three different spreadsheets were used: Sampling Data, Field Data and Questionnaire Responses. The spreadsheets were converted to ASCII, merged, and then converted to SAS (Statistical Analysis System) PC data files. The SAS PC software system was used throughout for all statistical analyses.[141] Statistical significance was defined as a probability of 1 percent or less. This conservative probability was chosen to adjust for the multiple endpoints being studied, hearing loss in both ears over four frequencies (3, 4, 6 and 8 kHz). Statistical summaries including frequency distributions, histograms, means, proportions and their standard errors were obtained for all of the numeric variables. Analysis of variance and the F-test were used to compare group means.

The principal outcome variables were the semi-continuous hearing loss levels at different frequencies, measured in decibels hearing level (dBHL). For each subject, at each frequency, 4 hearing loss measurements were taken: pre-shift left and right ear

and post-shift left and right ear. Acute effects of styrene and noise on hearing loss were assessed using the change in hearing over the shift (post- minus pre-shift) as the outcome variable and the personal noise and styrene exposure measurements obtained on the same day as predictor variables. Multiple regression analysis, using the SAS General Linear Models procedure (PROC GLM), was conducted with the pre-shift measurement of hearing used as a co-variate.

In order to examine chronic effects, various combinations of the 4 measurements were used, including, for each ear, the *best* of pre- or post-shift, whichever measure was numerically smaller, indicating the best acuity, and conversely, the *worst* between the pre- and post-shift measure. In addition, the left and right ear measurements were combined, either using the arithmetic means of the *best* and the *worst*, or using the highest or maximum value between left or right for each of the *best* and the *worst* measures. These variables were analyzed using analysis of variance and multiple linear regression. In these analyses, these hearing loss variables were examined both directly, as the measured values and as the natural logarithmic transformation of the measured values.

The data analysis was principally aimed at assessing possible ototoxic effects associated with long term, chronic exposures. The styrene and noise exposure measurements were obtained, for each subject, over a single day during the course of the investigation. This exposure can not be considered as representative of a working

lifetime exposure. However, for styrene, the current measured exposures were used, as arithmetic means over job categories, together with job classification histories and durations, to construct an exposure index or lifetime dose, for each subject. These lifetime exposures were adjusted to account for reduction in exposure achieved by reported use of respiratory protection. For noise exposure, the assignment of an exposure index for each subject was more difficult for several reasons. Noise exposures, of varying types, impulsive, continuous and intermittent, intensities and durations are associated with most industrial workplaces. Self assessment of noise exposure was found to be subjective and inconsistent. Consequently, the lifetime noise exposure index, for each subject, was established based on the measured data for the current job, as well as an estimate of previous exposures based on the professional judgement of occupational hygienists, together with durat : and adjustment for reported use of hearing protection. Further details regarding this exposure index and its refinement are given in Section 4.3.1.

The created exposure index variables of lifetime noise and styrene exposure and age were used either as categorical variables or factors in analysis of variance or as the actual values utilized in regression analyses. Additional factors of possible importance: smoking, occupational exposures to other solvents and recreational noise and chemical exposures, were included in these analyses. Based on the responses provided by each subject in the questionnaire, smoking was included as either a categorical variable, non-, previous or current smoker, or as a continuous variable

taking the product of the number of cigarettes smoked and duration. Occupational solvent and recreational noise and chemical exposures were included as continuous variables, as the sum of the total number of days per year reported spent at these activities, respectively.

Multiple regression analysis was conducted, assuming a linear relationship amongst the variables, except the styrene and noise lifetime exposures, which were transformed logarithmically. Most analyses were frequency specific, that is, were conducted separately for the outcome variable, hearing loss, at each frequency. Hearing loss was measured at 0.5, 1, 2, 3, 4, 6 and 8 kHz. The multiple regression analyses were conducted on all frequencies, but are reported only on the higher frequencies, 3 kHz and above, since the postulated ototoxic effects are in this range. The regression analyses were conducted on the full data set of 299 subjects. In addition, since the positive relationship between age and hearing loss is well known and hearing loss due to ageing becomes increasingly important after the age of 50, the analyses were also conducted on a subset of the data, which excluded the 37 subjects who were over 50 years of age, resulting in a subset of 262. In order to identify whether findings were influenced by individuals with substantial hearing loss, regression analyses were also conducted on a further subset of the data, excluding those individuals with mean hearing loss at 3 and 4 kHz or mean loss at 6 and 8 kHz of 50 dB HL or greater. Using this arbitrary criterion a further 19 subjects were excluded.

To the extent that styrene and/or noise exposure exert a similar effect across frequency ranges, hearing loss was also averaged (mid range: 3 and 4 kHz, and high range: 6 and 8 kHz), to obtain a more precise analysis, again using multiple regression.

For some analyses binary outcome variables, obtained from the semi-continuous variables by using a cut-off point, were used, that is, binary variables which defined individuals as being above or below some threshold such as 25 dB of hearing loss. These binary variables were analyzed with multiple logistic regression, using the SAS categorical data modelling procedure (PROC CATMOD). In addition, the binary variables were used in non-parametric analyses, using the Wilcoxon rank sum test.

The SAS Non Linear Regression procedure (PROC NONLIN) was used to examine the appropriateness of a non linear model for the styrene and noise exposure predictor variables. Best estimate combinations of slopes and exponents were determined for hearing loss at 4, 6 and 8 kHz and these combinations were then used in a multiple regression analysis including all predictor variables.

Multiple regression analyses were also used to assess the relative changes in hearing loss patterns between 3, 4, 6 and 8 kHz, by examining the relationships between the slopes of the audiogram curves at 3-4, 4-6 and 6-8 kHz.

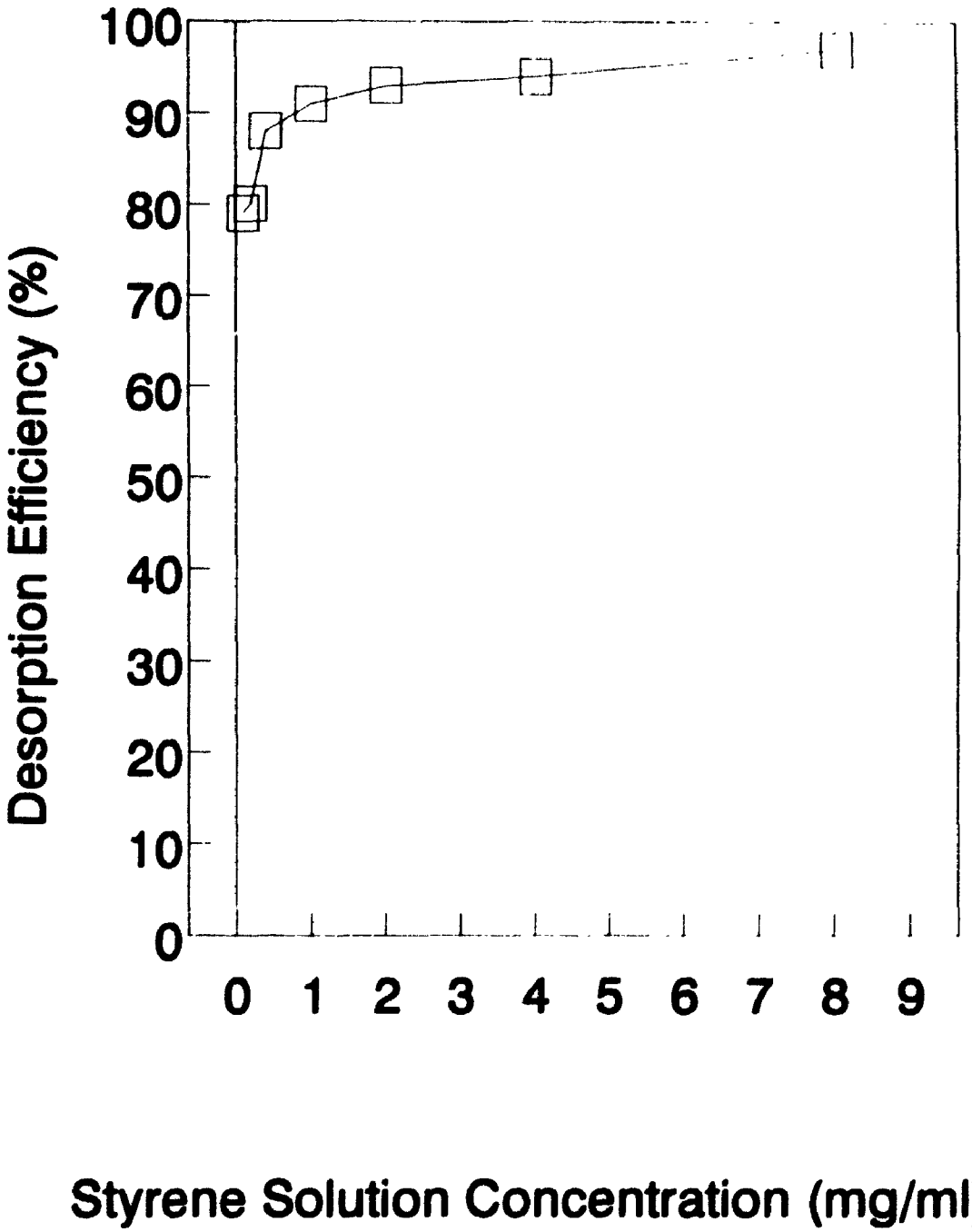
The relationship between self-reported hearing acuity and measured acuity, as a binary outcome variable, was examined for all subjects using chi square statistics as well as logistic regression analyses. Chi square statistics were also used to examine associations between measured hearing loss, as the binary outcome variable, and the responses to questions in which each subject was asked to rank his difficulty hearing in certain everyday situations (see Questionnaire, Appendix II).

Chi square statistics were used to identify significant relationships between current styrene exposures and reported symptoms, such as dizziness and nausea, reported separately for both at work and at home.

Table 3-1: CHROMATOGRAPHIC CONDITIONS FOR STYRENE ANALYSES

	HEWLETT PACKARD 5850	VARIAN 3400
Column	Metal 10' x 0.25" ID FFAP on 80/100 Chromosorb W[a]	Glass 4 m x 2 mm ID 10% FFAP on 80/100 Chromosorb W[a]
Temperature		
Oven	155 °C	155 °C
Injector	200 °C	200 °C
FID	250 °C	250 °C
Gases		
Carrier	N_2 @ 26.5 mL/min	He @ 26 mL/min
FID	H_2 @ 30 mL/min Air @ 300 mL/min	H_2 @ 30 mL/min Air @ 300 mL/min
Range	-	10
Attenuation	12	Auto
Injection volume	1 μL Manual	1 μL Autosampler
Run Time	4 minutes	4.5 minutes
Styrene Retention time	3.10 minutes	2.95 minutes

Figure 3–1: Desorption Efficiency Curve For Styrene



CHAPTER 4: RESULTS

4.1 GENERAL OVERVIEW OF DATA

A total of 299 male subjects from 14 fibreglass reinforced plastics manufacturing plants and one control location throughout southern Ontario and Nova Scotia were included in the study. The plants varied in size from those employing less than 5 workers to those with a workforce in excess of 100. The number of subjects drawn from each plant ranged from 2 to 60. Table 4-1 provides summary data for the mean age and styrene and noise exposures in each plant. The average age of all the subjects was 36.6. The age distribution is shown in Figure 4-1 (page 108). The means of the measured 8-hour TWA styrene exposures varied significantly between plants ($F=10.5$, $p<0.0001$) and individual values ranged from 0.5 mg/m^3 (the detection limit of the method) to 522 mg/m^3. The distribution of styrene exposures is graphically displayed in Figure 4-2 (page 109). Similarly, the means of the measured daily noise exposures varied significantly across plants ($F=3.82$, $p<0.0001$), with individual values ranging from an *Equivalent Sound Level* (L_{eq}) of 70.4 to 105.2 dB(A), (Figure 4-3, page 110). It should be noted that for a few subjects either the styrene or the noise exposure measurement was lost due to equipment malfunction. Although there were apparent differences in age, styrene and noise exposures between plants, these differences were not important in terms of the objectives of the study, since the purpose was to obtain a range of exposures.

Table 4-1: Summary Data by Plant

Plant	Location	n	Age[1]	Styrene[1]	Geom.[2]	Leq[1]
1	Toronto	29	33.0 ± 8.0	7.4 ± 13.2	1.4 ± 6.9	89.5 ± 5.5
2	Toronto	21	39.7 ± 10.2	102.9 ± 91.1	51.4 ± 8.3	87.5 ± 4.7
3	Nova Scotia	60	35.5 ± 10.4	45.8 ± 37.0	21.9 ± 6.2	86.2 ± 6.8
4	Nova Scotia	9	27.1 ± 6.7	221.5 ± 206.0	107.0 ± 4.5	86.0 ± 3.1
5	Nova Scotia	16	36.4 ± 7.9	112.7 ± 114.6	29.2 ± 13.5	87.0 ± 6.6
6	Nova Scotia	2	29.5 ± 6.4	274.8 ± 51.1	272.5 ± 1.2	84.7 ± 0.8
7	Nova Scotia	4	31.2 ± 13.4	-	--	--
8	Nova Scotia	5	31.0 ± 8.3	12.9 ± 11.8	6.0 ± 6.3	94.8 ± 6.8
9	Nova Scotia	3	45.3 ± 12.7	19.0 ± 7.7	18.0 ± 1.5	87.7 ± 2.2
10	Toronto	40	44.2 ± 11.7	120.0 ± 103.9	76.0 ± 3.0	89.2 ± 5.5
11	S.E Ontario	27	34.8 ± 9.0	58.1 ± 48.2	31.7 ± 4.4	88.6 ± 6.2
12	Toronto	8	42.4 ± 12.9	25.9 ± 20.2	16.8 ± 3.1	85.4 ± 5.1
13	S.E Ontario	48	31.8 ± 7.5	103.6 ± 75.6	64.6 ± 4.4	86.7 ± 7.6
14	Toronto	7	40.6 ± 7.4	-	-	-
15	S.E Ontario	20	43.2 ± 12.5	26.9 ± 18.8	21.9 ± 1.9	85.6 ± 5.4
Sum (n) and means		299	36.6 ± 10.7	73.5 ± 88.6	23.0 ± 9.6	87.2 ± 6.5
p-value[3]		-	0.0001	0.0001	0.0001	0.0001

1 - Arithmetic Mean ± Standard Deviation [styrene - mg/m^3; Leq - dB(A)]
2 - Styrene - Geometric Mean ± Standard Deviation
3 - Associated with F-test comparison of group means

In comparing the pre- with the post-shift audiogram at all frequencies for all subjects, it was found that the distribution of the change over shift (Post- minus Pre-shift) resembled a normal distribution, with a mean value of approximately 0. This is illustrated for the change in hearing loss at 4 kHz for all subjects (Figure 4-4, page 111). The magnitude of a chronic hearing loss at each frequency can be estimated

using the pre-shift measure, the post-shift measure or some combination of these: either the *best*, that is, smallest, measured hearing loss of the pre- or post-shift value; or, conversely the *worst* measured loss. For comparative purposes, the mean and standard deviation hearing losses, in decibels hearing level (dBHL), for all of the above combinations are given in Table 4-2.

Table 4-2: Mean Hearing Loss (# HL) using different measures (n=299)

MEASURE	Frequency/EAR							
	3 kHz		4 kHz		6 kHz		8 kHz	
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
Pre-shift	21 ± 19	20 ± 20	23 ± 21	25 ± 23	33 ± 22	32 ± 22	26 ± 22	31 ± 23
Post-shift	22 ± 19	19 ± 19	25 ± 21	24 ± 21	35 ± 21	31 ± 21	27 ± 22	30 ± 22
BEST[1]	18 ± 17	16 ± 18	21 ± 20	21 ± 20	30 ± 21	27 ± 20	23 ± 21	26 ± 21
WORST[2]	24 ± 20	24 ± 20	27 ± 22	27 ± 22	38 ± 21	37 ± 21	30 ± 22	30 ± 22

1 - Best = lower of pre- and post-shift HL measurement
2 - Worst = greater of pre- and post-shift HL measurement

The *best* hearing loss variable provides the most conservative measure and for most applications this variable was utilized. The distributions of *best* hearing loss, for illustrative purposes, in the left ear at 4, 6 and 8 kHz are given in Figures 4-5 to 4-7 (pages 112-114), respectively. The data clearly suggest lognormal distributions; therefore estimates of mean hearing losses and their precision were determined using both arithmetic and geometric mean and standard deviation values (Table 4-3). The proportion of subjects having hearing losses, defined as either HL > 25 dB or HL > 40 dB, is given in Figure 4-8 (page 115).

The average hearing loss, as the geometric mean of left and right ear and based on the best of pre- or post-shift audiogram, is presented in Figure 4-9 (page 116),

separately for four age groups (less than 30, 30 to 39, 40 to 49, and over 50 years). The differences in mean hearing loss across the four age categories were generally statistically significant for frequencies above 2 kHz. The differences between the two older age groups (40 - 49 and >50) at 4 and 6 kHz approached significance ($0.01 < p < 0.05$) and at 8 kHz, for those less than 30 years compared to those 30-39 years old, the difference was not significant ($p=0.14$). Thus, loss of hearing acuity was strongly influenced by age, with the occurrence of hearing loss increasing with advancing age. Consequently, the statistical analysis was conducted on both the full data set (n=299), as well as on a subset including only subjects less than 50 years of age (n=262).

Table 4-3: Mean Hearing Loss (dBHL) for all Subjects (*Best*) (n=299)

	3 kHz	4 kHz	6 kHz	8 kHz
LEFT[1]				
Arithmetic[2]	18.4 ±17.5	20.9 ± 20.0	30.2 ± 20.8	22.9 ± 20.9
Geometric[3]	6.6 ± 7.4	8.1 ± 7.4	20.1 ± 3.3	10.0 ± 6.0
RIGHT[4]				
Arithmetic	16.4 ± 17.7	20.9 ± 20.4	27.1 ± 20.4	26.4 ± 21.1
Geometric	5.4 ± 8.2	6.6 ± 9.0	18.2 ± 3.7	16.4 ± 4.5
AVG L/R[5]				
Arithmetic	17.4 ± 16.1	20.9 ± 18.6	28.6 ± 19.1	24.7 ± 19.5
Geometric	8.1 ± 5.5	11.0 ± 5.0	22.2 ± 2.5	16.4 ± 3.3

1 - Left Hearing Loss, minimum value (best) pre- or post-shift measure
2 - Arithmetic mean ± Standard Deviation
3 - Geometric mean ± Geometric Standard Deviation
4 - Right Hearing Loss, minimum value (best) pre- or post-shift measure
5 - Arithmetic mean of Left[1] and Right[4]

The study participants were classified by their job titles as either: *Directly Exposed* (laminators); *Indirectly Exposed* (assembly workers, foremen); and, *Not Exposed*. In their current jobs, 170 subjects were classified as Directly Exposed (DE), 86 as Indirectly Exposed (IE) and 43 as Not Exposed (NE). The arithmetic means of the measured TWA styrene exposures for the three groups were: DE 109, IE 36 and NE 11 mg/m^3, and were significantly different (F=40.0, p=0.0001), Table 4-4. For those classified as being DE, 58 percent had, on the day of sampling, styrene exposures below 100 mg/m^3 and only 15 percent greater than 200 mg/m^3. Ninety-four percent of the IE group and 100 percent of the NE group had styrene exposures of less than 100 mg/m^3 (Table 4-5).

Table 4-4: Styrene and Noise Exposure for Directly Exposed, Indirectly Exposed and Not Exposed Subjects

	Directly Exposed	Indirectly Exposed	Not Exposed	p[1]
n	170	86	43	
Age	36.0 ± 11.0	37.0 ± 10.6	38.4 ± 9.5	0.39
TWA Styrene[2]	108.7 ± 98.2	36.0 ± 49.0	10.7 ± 14.7	0.0001
GM TWA Styrene[3]	58.6 ± 5.1	12.8 ± 7.4	1.7 ± 16.7	0.0001
L_{eq}[4]	88.1 ± 5.3	89.2 ± 6.1	80.0 ± 7.0	0.0001

1 - p-value associated with the F-test comparison of three group means
2 - Time-weighted average styrene, mg/m^3 (arithmetic mean ± SD)
3 - Time-weighted average styrene, mg/m^3 (geometric mean ± SD)
4 - Equivalent sound level, dB(A), based on 3 dB exchange rate (Arithmetic mean ± SD)

Overall, the measured current noise exposures for the three groups were significantly different (F=40.4, p=0.0001). However, using t-tests comparing pairs of group means the Directly Exposed group and the Indirectly Exposed group were similar (p=0.15). However, the NE group had significantly lower noise exposure than either

of the other groups (p=0.0001, Table 4-4). Only 23 percent of the NE group had L_{eq} exposures greater than 85 dB(A), while 67 percent of the DE group and 74 percent of the IE group had L_{eq} noise exposures in excess of 85 dB(A)(Table 4-5).

Table 4-5: Noise, Styrene and Age Distribution Among the Three Exposure Classes

	Directly Exposed	Indirectly Exposed	Not Exposed	p*
n	170	86	43	
Noise				
<80 dB(A)	14 (8%)	8 (9%)	25 (58%)	
80-85 dB(A)	42 (25%)	14 (16%)	8 (19%)	
>85 dB(A)	114 (67%)	64 (74%)	10 (23%)	
	(100%)	(100%)	(100%)	0.000
Styrene				
<100 mg/m³	99 (58%)	81 (94%)	43 (100%)	
100-200	46 (27%)	4 (5%)	0 (0%)	
>200 mg/m³	25 (15%)	1 (1%)	0 (0%)	
	(100%)	(100%)	(100%)	0.000
Age				
<30	55 (32%)	23 (27%)	9 (21%)	
30-39	60 (35%)	31 (36%)	13 (30%)	
40-49	26 (15%)	17 (20%)	17 (40%)	
50-59	24 (14%)	13 (15%)	4 (9%)	
>60	5 (3%)	2 (2%)	0 (0%)	
	(100%)	(100%)	(100%)	0.299

* p-value associated with the Mantel-Haenszel χ^2 comparison of the class distributions in the three groups.

The ages of the workers in the three exposed groups were similar (Table 4-4). Although not significant, the Not Exposed group was slightly older; 51 percent were less than 40 and 40 percent between 40 and 49 ($MH\chi^2=1.08$, NS, Table 4-5).

In current jobs for each subject, the use of hearing protection and respiratory

protection can be compared with noise and styrene exposures, respectively. Of subjects having a noise exposure of less than 80 dB(A), 17 percent reported using hearing protection one half of the time or more (Table 4-6). However, 42 percent of those with exposures over 85 dB(A) reported this same level of use of the protection.

Table 4-6: Use of Hearing Protection and Measured Noise Exposure

Use of Hearing Protection (% time worn)	Measured Noise Exposure, Leq in dB(A)		
	< 80	80 - 85	> 85
0 % (Never)	57.4%	42.2%	29.3%
25 %	25.5%	43.8%	28.7%
50 %	4.3%	1.6%	13.1%
75 %	4.3%	6.2%	5.3%
100 % (Always)	8.5%	6.2%	18.6%
n	47 (100%)	64 (100%)	188 (100%)

Table 4-7: Use of Respiratory Protection and Measured Styrene Exposure

Use of Resp Protection (% time worn)	Measured Styrene Exposure, mg/m³		
	< 100	100 - 200	> 200
0 % (Never)	74.0%	62.0%	50.0%
25 %	19.7%	18.0%	38.5%
50 %	3.6%	14.0%	11.5%
75 %	0.5%	2.0%	0
100 % (Always)	2.2%	4.0%	0
n	223 (100%)	50 (100%)	26 (100%)

Although the group size was small (n=26), only 11 percent of those subjects exposed to greater than 200 mg/m^3 styrene reported wearing appropriate respiratory protection 50 percent of the time, or more (Table 4-7).

4.2 "ACUTE EFFECTS" ANALYSIS

Over the course of a single shift, as described above and illustrated in Figure 4-4 (page 111), at any frequency, subjects were as likely to have improved hearing acuity as reduced acuity. At each frequency, the means of the post-shift hearing loss minus pre-shift hearing loss, right and left ears separately, were not significantly different from zero, based on t-test statistics (Table 4-8), although several approached significance (p= 0.04 to 0.08). However, at all frequencies, hearing acuity in the right ear tended to improve over the shift, while the left ear tended to deteriorate. The findings (Table 4-9) when only those subjects less than 50 years of age were considered were similar.

Table 4-8: Post-shift minus Pre-shift Hearing Loss (dBHL), n =299

Frequency	Ear	Arithmetic Mean	Standard Deviation	Student's t-value	p-value
8 kHz	Left	0.56	9.9	0.95	0.34
	Right	-1.44	12.5	-1.92	0.06
6 kHz	Left	1.11	10.1	1.88	0.06
	Right	-1.39	12.9	-1.79	0.08
4 kHz	Left	1.32	10.8	2.08	0.04
	Right	-0.78	12.1	-1.07	0.29
3 kHz	Left	0.99	9.1	1.86	0.07
	Right	-1.05	11.2	-1.56	0.12

Table 4-9: Post-shift minus Pre-Shift Hearing Loss (dBHL) Age < 50, n=262					
Frequency	Ear	Arithmetic Mean	Standard Deviation	Student's t	p-value
8 kHz	Left	0.32	9.4	0.54	0.59
	Right	-1.71	12.4	-2.12	0.04
6 kHz	Left	1.32	9.9	2.11	0.04
	Right	-1.33	12.4	-1.66	0.10
4 kHz	Left	1.04	9.2	1.79	0.08
	Right	-0.56	11.5	-0.76	0.45
3 kHz	Left	0.94	7.9	1.88	0.06
	Right	-1.15	10.6	-1.67	0.10

The direction of the change in hearing loss over shift (positive = increased hearing loss; negative = decreased loss or improved acuity) was not related to whether the subjects had previous hearing tests or not. For example, at 4 kHz, 43 percent of those with a measured improved acuity over the shift had never had a hearing test which is similar to the 49 percent among those with a measured deterioration (Table 4-10).

Table 4-10: Relation of previous hearing test to change in hearing acuity 4 kHz (n=294)		
Previous hearing test	Change in Hearing Acuity over shift	
	Positive	Negative
Yes	51%	57%
No	49%	43%
n (Σ)	116 (100%)	178 (100%)

The change in hearing loss over shift (ΔHL) was found to be significantly dependent upon the pre-shift hearing loss at each frequency. Workers with higher pre-shift hearing loss were the ones who experienced, on average, the least change in hearing loss over the shift. Consequently, for multiple regression and analysis of covariance, the pre-shift hearing loss variable was used as a covariate.

Multiple regression analysis was conducted to examine the relationships between ΔHL and pre-shift hearing loss, age, styrene exposure, as the natural logarithmic transformation (lnSTY) and noise exposure (L_{eq}) and shift (Table 4-11).

Table 4-11: Regression Analyses of Acute Changes in Hearing (Post minus Pre shift) as a Function of Age and Exposures for all subjects, n=269[1]

Variable		Frequency (kHz)			
		8	6	4	3
Pre-Shift	β	-0.15	-0.15	-0.20	-0.20
	p	0.0001	0.0001	0.0001	0.0001
Age	β	0.18	0.11	0.25	0.23
	p	0.003	0.09	0.0001	0.0001
lnSTY	β	-0.18	0.02	0.10	0.13
	p	0.50	0.93	0.68	0.56
L_{eq}	β	-0.06	0.05	0.08	-0.05
	p	0.52	0.69	0.35	0.51

1 - All Subjects n = 299; regression analysis deletes subjects with any variable missing, therefore, actual n = 269

The shift variable was used to indicate the day of the work week that the sampling and testing was carried out. Typically, for plants operating five days per week, Monday to Friday, if sampling was done on Monday, the categorical variable *Shift* was

assigned a value of 1, for Tuesday *Shift* was 2, and so on. For plants operating on other schedules, the *Shift* variable was assigned, counting from the most recent weekend equivalent. Using the full data set, including all subjects (Table 4-11), both pre-shift HL and age were related to ΔHL, with pre-shift HL being negatively and age positively correlated. Overall, hearing loss was similar across the different shifts for all of the frequencies.

Additional regression analyses were conducted to assess the effect of the use of both hearing protection (HP) and respirators (RESP) on hearing loss, and to examine, using the respective interaction terms, whether their use moderated the effects of noise and styrene exposures.(Table 4-12) Noise exposure, as L_{eq}, HP and their interaction term were unimportant at all frequencies and were removed from the model.

Table 4-12: Regression Analyses of Acute Changes in Hearing (Post minus Pre shift, average of L and R ear) for all subjects, n=276[1]

Variable		Frequency (kHz)			
		8	6	4	3
Pre-Shift	β	-0.15	-0.15	-0.20	-0.19
	p	0.0001	0.0001	0.0001	0.0001
Age	β	0.22	0.13	0.24	0.23
	p	0.0002	0.02	0.0001	0.0001
lnSTY	β	1.18	3.62	0.27	0.24
	p	0.28	0.04	0.49	0.43
Resp[2]	p	0.18	0.49	0.37	0.54
lnSTY*Resp[2]	p	0.04	0.05	0.94	0.91

1 - All Subjects n = 299; regression analysis deletes subjects with any variable missing, therefore, actual n = 276

2 - Resp is a categorical variable with 5 categories, no overall β available, for slopes - see Table 4-13.

As previously demonstrated, pre-shift HL and age were significant factors. In addition, at 6 kHz the relationship between styrene exposure (lnSTY) and ΔHL approached significance (β=3.62, p=0.042). Further, the interaction term between respirator use and styrene exposure (RESP*lnSTY) was identified as approaching significance at 8 and 6 kHz (Table 4-12). Table 4-13 provides the slope estimates, for the relationships between ΔHL and styrene exposure, for each class of respirator use. These suggest that at 6 and 8 kHz, increased respirator use is associated with an increase in the effect of styrene on hearing loss, clearly not reasonable.

Table 4-13: Slope estimate for the relationship between HL and styrene exposure for each class of respirator use[1]

Respirator use class	Frequency (kHz)			
	8	6	4	3
0% - Never used	-0.44	-0.23	0.36	0.20
25% time	1.02	0.98	0.15	0.32
50% time	0.74	0.34	0.75	0.85
≥ 75% time	1.18	3.62	0.27	0.24

1 - Calculated, at each frequency, as the sum of the β estimate for lnSTY and the individual β estimate for the interaction at each level of respirator usage

4.3 LIFETIME NOISE AND STYRENE EXPOSURE INDICES

In order to consider the effects of chronic styrene and/or noise exposures on hearing loss, it was necessary to first construct a measure of chronic or cumulative exposure. In this study, TWA styrene and noise exposure measurements were taken for each subject on one day. Information, for each subject, was gathered through the questionnaire on current job, work histories, including chemical exposures, and self-reported noise exposure estimates. For both styrene and noise, current job category mean exposures were calculated (Table 4-4).

4.3.1 First Estimate of Noise and Styrene Exposure Indices

Initially, for each subject, cumulative lifetime styrene exposure was calculated by determining, from current and previous jobs, the total duration spent by the subject at each job category. The duration (months) spent in each category was multiplied by the corresponding mean exposure obtained in the three categories (DE, IE, NE) in the current job (mg/m^3-months). The total lifetime cumulative exposure was taken as the sum of these products.

For example, the lifetime styrene exposure, (Sty1) =

(Total duration as Laminator x 109 mg/m^3)
+ (Total duration as Assembly, etc x 36 mg/m^3)
+ (Total duration as Other x 11 mg/m^3)

Similarly, an initial lifetime noise exposure was calculated based on current noise exposures, L_{eq} for each job category: Laminator 88 dB(A), Assembly 89 dB(A) and Other 80 dB(A), taking into account the use of hearing protection. As described previously, self-reported use of hearing protection (HP), for each job (current and previous) was coded as:

Never Used	HP = 0
Used 25% of time	HP = 1
Used 50% of time	HP = 2
Used 75% of time	HP = 3
Always Used	HP = 4

The effectiveness of hearing protection in reducing noise exposures is a subject

of much debate and depends upon many factors, including the type and condition of the protector, how well it fits or is inserted, the level of use and the frequency distribution of the noise.[142] It is difficult to determine accurately the actual noise exposure for an individual wearing hearing protection and this becomes even more difficult retrospectively. Consequently, a conservative measure of effective noise exposure ($effL_{eq}$) was taken to be a 4 dB(A) reduction in L_{eq} for HP=4, 3 dB(A) reduction for HP=3, and so on, with no reduction for HP=0. The $effL_{eq}$ is in units of decibels, on a logarithmic scale, such that decibels equal $10 \log_{10}(p/p_o)^2$ where p is sound pressure in pascals (Pa) and p_o is the standard reference pressure of 0.00002 Pa. Because of this logarithmic scale, this variable, cannot be simply multiplied by duration to create a cumulative lifetime exposure. A new variable *intensity* was created by taking the antilog of $effL_{eq}$ (see Appendix III for the precise derivation). Specifically:

$$Intensity = 10^{[(effLeq)/10 - 12]}$$

As described above for styrene, intensity was then multiplied by duration spent at each job category. The sum of the products was taken as a lifetime noise exposure that is indicative of the total sound energy impacted on the subject over his working lifetime (**Noise1**).

Multiple regression analysis was conducted to examine the effects of the variables age, lifetime cumulative styrene exposure (**Sty1**) and noise exposure,

or total sound energy (Noise1). The distribution of these two exposure variables was skewed; therefore, their natural logarithmic transformations were used. Thus, the model under examination was:

$$HL = \beta_1 + \beta_2 \text{ Age} + \beta_3 \text{ lnTSty1} + \beta_4 \text{ lnNoise1}$$

The model was examined using the *Best* hearing loss, separately for the left and right ears (Table 4-14).

Table 4-14: Regression analyses of the association between Hearing Loss and Age, Styrene and Noise exposure - USING FIRST ESTIMATE

HEARING LOSS BY FREQUENCY	Age		lnTsty1[1]		lnNoise1[1]	
	β	p	β	p	β	p
8 Left	0.91	0.0001	2.31	0.08	-1.13	0.39
8 Right	1.00	0.0001	2.38	0.06	-0.57	0.65
6 Left	0.84	0.0001	2.03	0.13	-0.31	0.81
6 Right	0.90	0.0001	2.32	0.07	-0.58	0.64
4 Left	0.97	0.0001	3.00	0.03	-1.49	0.21
4 Right	1.06	0.0001	1.61	0.18	-0.44	0.72
3 Left	0.87	0.0001	1.94	0.06	-0.75	0.47
3 Right	0.99	0.0001	1.28	0.21	-0.83	0.41

1 - Natural logarithmic transformation of the first estimates of lifetime styrene and noise exposure indices

Age was found to be a highly significant variable for hearing loss at all frequencies. Styrene exposure (lnTSty1) approached significance as a contributor to hearing loss at each frequency, yet noise exposure (lnNoise1) was conspicuously absent as an important variable throughout. As it is well known that chronic noise exposure is associated with increased hearing loss (noise-induced hearing loss), it was felt that the basis for the noise exposure index calculation required re-evaluation.

4.3.2 Second Estimate of Noise and Styrene Exposure Indices

For both current and all previous jobs, subjects were asked, as part of the questionnaire (Appendix II), two questions relating to noise exposure.

1. *Do you think you are (or were) exposed to excessive noise on this (that) job? (Variable = 'NOPIN')*
   Yes /__/ or No /__/

2. *If so, how would you describe the noise?*
   (Variable = 'NTIM')
   Constantly loud /__/ or Periodically loud /__/

These two variab0les were used to develop a second estimate of cumulative lifetime noise exposure, such that for each job, current and all previous, if *NOPIN* was answered as 'No', a job noise exposure of 80 dB(A) was assigned. For *NOPIN* 'yes' and *NTIM* 'periodic' the assigned noise exposure was 85. For *NOPIN* 'yes' and *NTIM* 'constant', the assigned value was 90. As described in Section 4.3.1, corrections were made for use of hearing protection to determine $effL_{eq}$, and total sound energy or lifetime noise exposure (Noise2) was calculated.

Using the styrene lifetime exposure index from the first estimate and Noise2, the multiple regression analyses were repeated, with essentially the same results. Styrene (as lnTsty1) appeared to be an important contributor, at certain frequencies; however, noise exposure (lnNoise2) did not appear to contribute to hearing loss (Table 4-15).

Table 4-15: Regression analyses of the association between Hearing Loss and Age, Styrene and Noise Exposures USING THE SECOND ESTIMATE

HEARING LOSS BY FREQUENCY	Age		lnTsty1[1]		lnNoise2[1]	
	β	p	β	p	β	p
8 Left	0.92	0.0001	2.41	0.07	-1.41	0.27
8 Right	1.02	0.0001	2.77	0.03	-1.45	0.25
6 Left	0.84	0.0001	2.11	0.10	0.14	0.91
6 Right	0.90	0.0001	2.33	0.06	-0.65	0.60
4 Left	0.97	0.0001	2.95	0.01	-1.49	0.21
4 Right	1.06	0.0001	1.64	0.17	-0.54	0.65
3 Left	0.88	0.0001	1.86	0.07	-0.62	0.54
3 Right	0.99	0.0001	1.24	0.22	-0.80	0.42

1 - Natural logarithmic transformation of the second estimates of styrene and noise exposure indices

In order to examine the validity of the noise exposure variable, the responses of each subject to Question 1 (above), for the current job, were compared with the actual measured noise exposure for that job. Using 85 dB(A) as the cutoff between noise exposure and not, the sensitivity of the affirmative response to detect actual exposures above 85 dB(A) was 71 percent. Only 52 percent of those with measured $L_{eq} < 85$ dB(A) reported 'no' for *NOPIN* (Table 4-16A).

Table 4-16A: Validity of Questionnaire Responses for noise exposure, using 85 dB(A) cutoff

Actual Exposure dB(A)	RESPONSE[1]	
	Nopin = YES	Nopin = NO
≥ 85	71%	48%
< 85	29%	52%
n (Σ)	193 (100%)	106 (100%)

1 - Question: Do you think you are exposed to excessive noise on this job? Response: Yes or No (Variable '*NOPIN*')

Using a cutoff of 80 dB(A), the corresponding sensitivity was 91 percent and the specificity, 27 percent (Table 4-16B). However, as 80 dB(A) is considered a low noise exposure, with very little risk of hearing loss associated with a lifetime exposure[95], this is of limited value.

Table 4-16B: Validity of Questionnaire Responses for noise exposure, using 80 dB(A) cutoff

Actual Exposure dB(A)	RESPONSE[1]	
	Nopin = YES	Nopin = NO
≥ 80	91%	73%
< 80	9%	27%
n (Σ)	192 (100%)	107 (100%)

1 - Question: Do you think you are exposed to excessive noise on this job? Response: Yes or No (Variable '*NOPIN*')

Taking into account the responses to both questions regarding noise exposures, the inability of the questionnaire responses to predict noise exposures is again apparent. Twenty-three percent of those reporting 'no' for *NOPIN* had L_{eq} exposures in excess of 90 dB(A) (Table 4-16C).

Table 4-16C: Validity of Questionnaire Responses regarding noise exposure, using 80 & 90 dB(A) cutoff

Actual Exposure dB(A)	RESPONSE[1,2]		
	Nopin = Yes Ntim = C	Nopin = Yes Ntim = P	Nopin = No
> 90	49%	36%	23%
80 - 90	46%	53%	50%
< 80	5%	11%	27%
n (Σ)	53 (100%)	140 (100%)	106 (100%)

1 - Question: Do you think you are exposed to excessive noise on this job? Response: Yes or No (Variable '*NOPIN*')
2 - Additional Question: If so, how would you describe the noise: Response: Constantly loud or Periodically loud (Variable: *NTIM*)

Furthermore, simple regression analysis, of the relationship between self reported and measured noise exposure revealed a Pearson correlation coefficient of 0.16.

4.3.3 Third Estimate of Noise and Styrene Exposure Indices

It was clear from the above, that the questionnaire responses were of limited value in predicting noise exposures in current jobs and, likely, even less accurate for previous positions. Therefore, an alternate approach to determining the cumulative lifetime noise exposure was devised. Each subject's file was reviewed, independently, by the two experienced occupational hygienists who had collected the original data. Two new (*Expert-rated exposure*) variables were created, *NCLASS* and *PTIM*, where:

NCLASS - Noise level estimate
L = low (80 dBA or less)
M = moderate (around 86 dBA)
H = high (above 90 dBA), and

PTIM - Occasional high spikes or peaks
Y = occasional peaks
N = noise level relatively constant

Within the questionnaires, each subject was asked a number of questions regarding previous employment, including name and type of employer, and a brief description of the job (job title). Using this information, the hygienists categorized each job for the two new variables, based on their knowledge of workplaces. The ratings for the two variables were done consistently for the

typical positions. In order to prevent bias, all ratings and assessments were carried out without information on the hearing loss status of each subject.

The two new variables were combined in a procedure similar to that used in the Second Estimate of lifetime dose. The assigned exposures, below, were selected somewhat arbitrarily, starting with 80 dB(A) which is considered to be an exposure, over a working lifetime, thought not to result in noise induced hearing loss in the vast majority of individuals.[95] The increase of 3 dBA was selected since this represents a doubling of sound energy. Thus, the exposures were assigned according to:

NCLASS	*PTIM*	ASSIGNED EXPOSURE
low	no	80 dBA
low	yes	83
moderate	no	86
moderate	yes	89
high	no	92
high	yes	95

As described in Section 4.3.1, corrections were made for use of hearing protection to determine $effL_{eq}$, and total sound energy or noise exposure (Noise3) calculated, based on these *Expert Rated* noise exposures. Using simple regression analysis, modelling the current *Expert Rated* noise exposure to the actual measured exposure, the Pearson Correlation Coefficient was found to be a much improved 0.68.

A refinement was also made to the method of determining lifetime styrene

exposure. Since there were significant differences in stryene exposures between plants, the styrene exposure level (mg/m^3) for the current job was taken as the mean for all subjects in the same plant in the same job category or type. That is, the exposure for a Laminator (Jobtype = DE) in plant 10, was the mean styrene exposure of all DE subjects in plant 10. For Not Exposed (NE) subjects, the styrene exposure was assessed as zero. For all previous jobs, DE were assigned 109 mg/m^3, IE 36 mg/m^3, and NE as zero. The only exception was for those subjects who had a previous job in one of the study plants. Their styrene exposures, were then based on the job type mean in that plant. The exposure, for each job position, was corrected for respirator use (RESP), which was coded in a manner similar to HP (Section 4.3.1, page 72). The styrene exposure was multiplied by a correction factor of (5 - RESPUSE)/5. For those always using a respirator, this resulted in a 80 percent reduction in the styrene exposure. As described in Section 4.3.1 for each position, the exposure derived above was multiplied by the duration and these were summed for each subject, resulting in a lifetime exposure estimate (Sty3).

The multiple regression analyses were repeated, using these calculated noise and styrene lifetime exposures, with considerably different results. In addition to age, the natural logarithmic transformation of lifetime noise exposure (lnNoise3) became or approached significance across all frequencies (Table 4-

17). In contrast, styrene lifetime exposure (Sty3), as the natural logarithmic transformation (lnTsty3), was found to be an insignificant contributor to hearing loss except at 6 kHz, left ear, which approached significance.

Table 4-17: Regression Analyses of the association between Hearing Loss and Age, Styrene and Noise Exposures USING THIRD ESTIMATE (All subjects, n=292)

HEARING LOSS BY FREQUENCY	Age		lnTsty3[1]		lnNoise3[1]	
	β	p	β	p	β	p
8 Left	0.81	0.0001	0.05	0.90	2.85	0.03
8 Right	0.93	0.0001	0.21	0.57	2.64	0.04
6 Left	0.81	0.0001	0.70	0.07	2.14	0.10
6 Right	0.81	0.0001	0.29	0.43	2.93	0.02
4 Left	0.88	0.0001	0.57	0.11	2.56	0.03
4 Right	0.93	0.0001	0.05	0.87	3.21	0.007
3 Left	0.76	0.0001	0.33	0.28	3.00	0.003
3 Right	0.93	0.0001	0.17	0.57	1.46	0.15

1 - Natural logarithmic transformation of the third estimates of styrene and noise exposure indices

Lifetime cumulative styrene exposure (Sty3), for all subjects ranged from 0 to 53,275 $mg.m^{-3}$.months, with a mean of 5,848. Values of 0 were changed to 0.1 to allow for logarithmic transformation. The frequency distribution, for subjects of age less than 50 is given in Figure 4-10A (page 117), with the natural logarithmic transformation of the styrene total lifetime exposure (lnTsty3) in Figure 4-10B (page 118). The mean of lnTsty3, for all subjects was 6.88 (SD=3.2). The lifetime total sound energy or noise exposure (Noise3), for all subjects ranged from 0.00016 to 0.66314 $watts.m^{-2}$.months, with a mean of 0.0815. The frequency distribution (subjects age <50) for lifetime total noise exposure is given in Figure 4-11A (page 119). The mean

natural logarithmic transformation (lnNoise3) of the total noise exposure was -3.03 (SD=1.12), Figure 4-11B (page 120).

4.4 "CHRONIC EFFECTS" ANALYSIS

4.4.1 Simple Regression and Nonparametric Analyses

Simple regression analyses were conducted on three models:

$$HL = \beta_1 + \beta_2 \text{ lnTsty3}$$
$$HL = \beta_1 + \beta_2 \text{ Age}$$
$$HL = \beta_1 + \beta_2 \text{ lnNoise3}$$

for the left and right ears, separately. In each case, the individual variable in the model was highly significant. In order to examine the degree of correlation among the three variables, Pearson correlation coefficients were determined. Recognizing that the variables may not be normally or lognormally distributed, the nonparametric Spearman rank order correlation coefficients were also calculated (Table 4-18).

Table 4-18: Correlation Analysis between Age, Noise Exposure and Styrene Exposure

VARIABLES	PEARSON COEFFICIENT		SPEARMAN COEFFICIENT	
	r	probability	r	probability
Age - lnTsty3	0.158	0.006	0.316	0.0001
Age - lnNoise3	0.546	0.0001	0.550	0.0001
lnTsty3 - lnNoise3	0.525	0.0001	0.602	0.0001

The high degree of correlation between the variables Age-lnNoise3 and the two exposure variables, lnTsty3 - lnNoise3, emphasizes the importance of not

relying on simple regression analyses.

Regression analyses, on the models relating only two variables to hearing loss:

$$HL = \beta_1 + \beta_2 \text{ Age} + \beta_3 \text{ lnNoise3}$$
$$HL = \beta_1 + \beta_2 \text{ Age} + \beta_3 \text{ lnTsty3}$$

gave similar results; age was significantly related to hearing loss at all frequencies above 2 kHz. lnNoise3 and lnTsty3 were, in their respective models, also highly significant. No substantial changes were noted in the above results when only the subjects of age less than 50 were included in the analysis.

4.4.2 Multiple Regression Analyses

4.4.2.1 Linear assumptions using 'best' hearing loss

In addition to the 3 key variables discussed above, (Age, lnTsty3 and lnNoise3) a number of other potentially relevant variables, determined from questionnaire responses, were included in a regression analysis. Smoking history was accounted for using one of two possible variables. Either a categorical variable (*SMK*): never smoked (N), previous smoker (P), or current smoker (Y), or a quantified variable (*Cigyr*), the reported number of cigarettes smoked per day times the number of years smoked, was used (Figure 4-12, page 121). A measure of recreational exposure to chemicals, including principally solvents, (*RCh*) was defined as the sum of the total number of days per year reported spent at painting, using glues or photography

darkroom work (Figure 4-13, page 122). Recreational exposures to noise (*RN*) were similarly estimated as the number of days using firearms (target shooting, hunting), snowmobiling, motorcycling, playing in a band or attending rock concerts, disco bars, and carpentry work (Figure 4-14, page 123). In addition, occupational exposures to other solvents (*Solv*) was approximated by taking the sum of the reported durations of exposures to acetone, methylene chloride, mineral spirits and paints (Figure 4-15, page 124). Thus, assuming a linear relationship amongst all the variables, the model under examination was:

$$HL = \beta_1 + \beta_2\ Age + \beta_3\ lnTsty3 + \beta_4\ lnNoise3 + \beta_5\ Cigyr$$
$$+ \beta_6\ RCh + \beta_7\ RN + \beta_8\ Solv$$

Age and lifetime noise exposure (lnNoise3) were important variables in determining HL, using the Age Exclusion data set, with noise exposure approaching significance at 3 and 4 kHz (Table 4-19A). Lifetime styrene exposure (lnTsty3) was not a significant factor. The squared Correlation Coefficients (R^2 values) for these regression models, which include all possible variables, ranged from 0.13 to 0.25. The number of cigarette years (*Cigyr*) was a significant factor for HL at 6 kHz in the right ear ($p=0.007$, $\beta=0.01$), as was recreational noise exposure ($p=0.01$, $\beta=-0.02$), although the negative slope estimate suggests a protective effect (Table 4-19B). Recreational chemical exposures only approached significance at 4 kHz (Left $p=0.02$, $\beta=0.06$). Other occupational solvent exposures approached significance in the

model at 6 kHz, left ear (p=0.06, β=-0.02), with a negative slope estimate.

Table 4-19A: Regression Coefficients and Associated p-values for Age, Styrene and Noise Exposures using Regression Analysis[1] Subjects Age <50 (n=256[2])

HEARING LOSS BY FREQUENCY	Age		lnTsty3		lnNoise3		R^2
	β	p	β	p	β	p	
8 Left	0.43	0.01	-0.15	0.71	2.23	0.12	0.13
8 Right	0.46	0.004	-0.27	0.48	2.71	0.048	0.15
6 Left	0.7	0.0001	0.58	0.15	2.17	0.13	0.19
6 Right	0.44	0.005	-0.13	0.72	3.08	0.022	0.22
4 Left	0.82	0.0001	0.48	0.18	2.71	0.04	0.25
4 Right	0.74	0.0001	-0.26	0.47	3.17	0.01	0.24
3 Left	0.66	0.0001	0.34	0.26	2.79	0.01	0.25
3 Right	0.71	0.0001	-0.02	0.93	1.86	0.07	0.22

1 - Regression Model: $HL = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTSty3 $+ \beta_4$ lnNoise3 $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

2 - 262 Subjects were less than 50 years of age; however, due to missing data, n=256

Table 4-19B: Regression Coefficients and Associated p-values for Smoking, Recreational Noise & Chemical and Occupational Solvent Exposures using Regression Analysis[1] Subjects Age <50 (n=256)

HEARING LOSS BY FREQUENCY	Cigyr		Rec Noise		Rec Chem		Solvent	
	β	p	β	p	β	p	β	p
8 Left	0.01	0.10	-0.01	0.49	-0.02	0.52	-0.001	0.89
8 Right	0.01	0.17	-0.01	0.20	-0.01	0.72	-0.002	0.81
6 Left	0.01	0.12	-0.003	0.72	-0.01	0.64	-0.02	0.06
6 Right	0.01	0.007	-0.02	0.01	-0.01	0.81	-0.005	0.63
4 Left	-0.001	0.87	0.003	0.74	0.06	0.02	-0.002	0.83
4 Right	0.004	0.31	-0.003	0.74	0.01	0.69	-0.003	0.73
3 Left	-0.001	0.93	-0.001	0.95	0.03	0.13	-0.006	0.44
3 Right	-0.001	0.92	-0.001	0.93	-0.01	0.80	-0.01	0.12

1 - Regression Model: $HL = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTSty3 $+ \beta_4$ lnNoise3 $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

In order to examine whether a few subjects with particularly large hearing

losses were influencing these regression analyses, a hearing loss exclusion was applied to the data set consisting of those less than 50 years of age. Using the criteria of either a mean hearing loss (best) between 3 and 4 kHz or between 6 and 8 kHz greater than 50 dBHL, 21 further subjects were excluded from the analysis (n=237). The results were generally similar: age was highly significant and noise exposure (as LnNoise3) was also important. However, styrene exposure (lnTsty3) approached significance as a contributor to HL in the left ear at 6 kHz (p=0.02, β=0.77) and at 4 kHz (left: p=0.06, β=0.59) (Table 4-20A). At 6 kHz, smoking remained a significant factor for hearing loss (p=0.001, β=0.01), as did recreational noise exposure (p=0.01, β=-0.02). Recreational chemical exposures were signficant at 4 kHz and approached significace at 3 kHz, while occupational solvent exposure was not significant (Table 4-20B).

Table 4-20A: Regression Coefficients and Associated p-values for Age, Styrene and Noise Exposures using Regression Analysis[1]
Subjects Age <50, Mean HL (3-4,6-8) <50 (n=237)

HEARING LOSS BY FREQUENCY	Age		lnTsty3		lnNoise3		R^2
	β	p	β	p	β	p	
8 Left	0.14	0.23	0.19	0.55	1.33	0.23	0.10
8 Right	0.25	0.06	0.01	0.99	2.16	0.05	0.12
6 Left	0.44	0.0008	0.77	0.02	1.65	0.13	0.19
6 Right	0.23	0.06	0.09	0.76	2.56	0.0008	0.22
4 Left	0.62	0.0001	0.59	0.06	1.98	0.07	0.26
4 Right	0.55	0.0001	0.13	0.67	2.932	0.03	0.23
3 Left	0.48	0.0001	0.43	0.11	2.24	0.02	0.24
3 Right	0.56	0.0001	0.23	0.36	1.35	0.13	0.21

1 - Regression Model: $HL = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTSty3 $+ \beta_4$ lnNoise3 $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

Table 4-20B: Regression Coefficients and Associated p-values for Smoking, Recreational Noise and Chemical and Occupational Solvent Exposures using Regression Analysis[1]
Subjects Age <50, Mean HL (3-4, 6-8) <50 (n=237)

HEARING LOSS BY FREQUENCY	Cigyr		Rec Noise		Rec Chem		Solvent	
	β	p	β	p	β	p	β	p
8 Left	0.006	0.12	-0.003	0.61	-0.01	0.82	0.01	0.15
8 Right	0.01	0.11	-0.01	0.33	0.001	0.99	-0.002	0.97
6 Left	0.01	0.14	-0.001	0.88	0.001	0.97	-0.01	0.19
6 Right	0.01	0.001	-0.02	0.01	0.004	0.87	-0.005	0.66
4 Left	-0.003	0.34	0.004	0.57	0.08	0.001	0.007	0.32
4 Right	0.004	0.22	0.001	0.92	0.02	0.38	0.001	0.88
3 Left	-0.001	0.65	-0.001	0.92	0.04	0.03	0.001	0.89
3 Right	0.001	0.71	0.001	0.93	-0.001	0.98	-0.01	0.08

1 - Regression Model: $HL = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTSty3 $+ \beta_4$ lnNoise3 $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

In order to determine if interactions occurred between the three important variables, multiple regression analyses were conducted including in the model the previous predictor variables, as well as the three possible interaction terms: Age*lnNoise3, Age*lnTsty3 and lnTsty3*lnNoise3. Significant interactions were found between Age and Noise exposure (lnNoise3), using the full data set, including all subjects (Table 4-21). When the interaction terms were included in the regression model, the slope estimate for lnNoise3 became negative. However, the overall slope estimate for lnNoise3, determined by taking the slopes for both the variable lnNoise3 as well as the interaction term, became a positive value past a given age (Table 4-21). Thus the influence of noise exposure on hearing loss appears to be significantly strengthened with increasing age. No significant interactions were found between styrene and noise exposures (lnTsty3 and lnNoise3), or between styrene exposure and age.

Table 4-21: Slope Estimates for *lnNoise3*, taking into account interaction between age and noise (All subjects, n=359)

Frequency/ Ear	p-value Age*Noise	Slope estimate for *lnNoise3* variable	Age for $\beta>0$
8 kHz LEFT	0.002	β = -7.7 + 0.34(Age)	23
RIGHT	0.087	β = -4.0 + 0.18(Age)	22
6 kHz LEFT	0.009	β = -6.5 + 0.28(Age)	23
RIGHT	0.22	---	--
4 kHz LEFT	0.049	β = -4.4 + 0.19(Age)	23
RIGHT	0.076	β = -4.9 + 0.17(Age)	28
3 kHz LEFT	0.0005	β = -7.0 + 0.29(Age)	24
RIGHT	0.013	β = -5.1 + 0.21(Age)	24

Considering only those subjects less than 50 years of age, the results were similar, with significant interactions between age and noise. In addition, at 4 kHz in the right ear, an interaction was observed between the Noise and Styrene exposure variables (Table 4-22).

Table 4-22: Slope Estimates for *lnNoise3*, taking into account interaction between age and noise (Age <50, n=256)

Frequency/ Ear	p-value Age*Noise	Slope estimate for *lnNoise3* variable	Age for $\beta>0$
8 kHz LEFT	0.079	β = -4.9 + 0.25(Age)	20
RIGHT	0.35	---	--
6 kHz LEFT	0.056	β = -6.4 + 0.28(Age)	23
RIGHT	0.43	---	--
4 kHz LEFT	0.009	β = -8.5 + 0.34(Age)	25
RIGHT*	0.084	* β = -6.4 + 0.22(Age) + 0.54(lnTsty3)	29*
3 kHz LEFT	0.007	β = -6.5 + 0.29(Age)	22
RIGHT	0.19	---	--

* A significant interaction was also found between lnNoise3 and lnTsty3 ($p=0.034$), therefore the styrene exposure interaction is included in the overall slope calculation

The three key variables, age and lifetime noise and styrene exposures, were modified to create categorical variables. Subjects less than 50 years of age were divided into three tertiles; and the noise and styrene lifetime exposure dose indices, each into quartiles. Least square means of hearing loss were determined within each combination of the age and noise exposure categories (Table 4-23A) and also, age-adjusted, within each combination of noise and styrene exposure categories (Tables 4-23B). The mean hearing losses are reported for the left ear at 6 kHz, for illustrative purposes. The significant, positive relationship between age and hearing loss is demonstrated in Table 4-23A. Generally, in each of the 4 noise exposure classes, and also, clearly in the marginal means, hearing loss increased with increasing age. The positive association between noise exposure and hearing loss was also evident.

Table 4-23A: Mean Hearing Loss (dBHL), 6 kHz[1]

AGE TERTILES	NOISE EXPOSURE QUARTILES				MARGINAL MEANS
	0	1	2	3	
0	18.9 [38]	16.4 [28]	26.2 [1-]	23.1 [8]	21.2 [87]
1	18.8 [17]	28.6 [21]	26.0 [30]	25.2 [23]	24.7 [91]
2	22.5 [10]	30.9 [17]	41.3 [23]	41.0 [34]	33.9 [84]
MARGINAL MEANS	20.1 [65]	25.3 [66]	31.1 [66]	30.0 [65]	– [262]

1 - Left ear HL [# subjects]

Table 4-23B illustrates the increasing hearing loss with increased noise exposure, independent of styrene exposure. In addition, the lack of a significant relationship between hearing loss and styrene exposure is evident. Although the number of subjects in each of the age tertiles and in the exposure

quartiles were the same, the actual sample sizes in each of the combination cells were different.

Table 4-23B Age-adjusted Least Squares Hearing Loss, 6 kHz[1]

STYRENE QUARTILES	NOISE EXPOSURE QUARTILES				MARGINAL MEANS
	0	1	2	3	
0	19.7 [33][1]	24.3 [16]	36.7 [10]	18.4 [6]	24.8 [65]
1	24.5 [15]	26.8 [24]	29.8 [19]	41.0 [8]	30.6 [66]
2	25.9 [14]	21.8 [16]	32.8 [23]	28.0 [13]	27.1 [66]
3	31.3 [3]	27.9 [10]	22.2 [14]	30.1 [38]	27.9 [65]
MARGINAL MEANS	25.4 [65]	25.2 [66]	30.4 [66]	29.4 [65]	-- [262]

1 - Left ear HL [# Subjects]

Hearing loss can be conveniently classified as high (6 and 8 kHz), medium (3 and 4 kHz) and low (2 kHz and below) frequency loss, calculated for each ear, by taking the mean of the *best* hearing losses. Results of multiple linear regression analyses were essentially similar to the results of the regression analyses for each frequency separately (Table 4-24). Age and noise exposure (lnNoise3) remained significant variables for medium and high frequency hearing loss. Styrene exposure (lnTsty3) was an insignificant contributor to hearing loss in both frequency ranges. Recreational noise exposure appeared to be a significant variable in the high frequency range for the right ear only. However, the slope estimate was less than zero, indicating an inverse relationship between HL and recreational noise exposure.

Table 4-24: Regression Coefficients and Associated p-values for the model including all predictors[1] using mean HL

VARIABLE: p-Value and slope estimate		High Frequency 6 & 8 kHz		Medium Frequency 3 & 4 kHz	
		LEFT	RIGHT	LEFT	RIGHT
Age	p	0.0003	0.002	0.0001	0.0001
	β	0.57	0.45	0.74	0.73
lnTsty3	p	0.57	0.56	0.18	0.64
	β	0.21	-0.20	0.41	-0.14
lnNoise3	p	0.097	0.02	0.01	0.02
	β	2.20	2.90	2.75	2.52
Cigyr	p	0.085	0.03	0.89	0.57
	β	0.008	0.009	-0.001	0.002
Rec Noise	p	0.57	0.04	0.87	0.81
	β	-0.004	-0.02	0.001	-0.001
Rec Chem	p	0.55	0.74	0.04	0.91
	β	-0.02	-0.009	0.05	0.003
Solvent	p	0.28	0.69	0.62	0.34
	β	-0.01	-0.003	-0.004	-0.01
R^2		0.17	0.21	0.28	0.26

Recreational chemical exposures appeared to be positively correlated with hearing loss in only the left ear at the medium frequency range. Smoking was an important contributor to hearing loss in both ears in the high frequencies.

4.4.2.2 Linear assumptions using 'worst' hearing loss

As described previously (Section 4.1), subjects were equally likely to have improved as reduced hearing acuity over the course of a single shift. The 'best' measured loss, as the more conservative estimate, was used for data analysis. However, for comparative purposes, the multiple regression analysis

was conducted using the '*worst*' hearing loss values and the age exclusion (age < 50) data set (Table 4-25A).

Table 4-25A: Regression Coefficients and Associated p-values for Age, Styrene and Noise Exposures using Regression Analysis[1] on WORST[3] HL Subjects Age <50[2] (n=256)

HEARING LOSS BY FREQUENCY	Age		lnTsty3		lnNoise3		R^2
	β	p	β	p	β	p	
8 Left	0.52	0.004	-0.23	0.59	2.98	0.05	0.13
8 Right	0.60	0.0009	-0.16	0.71	2.61	0.08	0.14
6 Left	0.79	0.0001	0.64	0.11	1044	0.32	0.19
6 Right	0.77	0.0001	0.59	0.14	1.73	0.23	0.19
4 Left	0.89	0.0001	0.58	0.13	2.73	0.04	0.25
4 Right	0.88	0.0001	0.60	0.12	2.86	0.04	0.24
3 Left	0.68	0.0001	0.23	0.50	3.42	0.006	0.21
3 Right	0.72	0.0001	0.25	0.47	3.39	0.007	0.22

1 - Regression Model: $HL^3 = \beta_1 + \beta_2$ Age + β_3 lnTSty3 + β_4 lnNoise3 + β_5 Cigyr + β_6 RCh + β_7 RN + β_8 Solv

2 - 262 Subjects were less than 50 years of age; however, due to missing data, n=256

3 - HL based on worst of pre- or post-shift measure

Age was a statistically significant contributor to hearing loss, and noise exposure as lnNoise3 was significant at 3 kHz and approached significance at 4 and 8 kHz. Styrene exposure (lnTsty3) was statistically nonsignificant. Recreational chemical exposure approached significance at 4 and 3 kHz for both the left and right ears. Smoking (as Cigyrs), recreational noise and occupational solvent exposures were not statistically significant (Table 4-25B).

Table 4-25B: Regression Coefficients and Associated p-values for Smoking, Recreational Noise & Chemical and Occupational Solvent Exposures using Regression Analysis[1] on WORST[2] HL Subjects Age <50 (n=256)

HEARING LOSS BY FREQUENCY	Cigyr		Rec Noise		Rec Chem		Solvent	
	β	p	β	p	β	p	β	p
8 Left	0.004	0.42	-0.004	0.66	-0.03	0.41	-0.002	0.83
8 Right	0.003	0.49	-0.002	0.77	-0.03	0.35	-0.003	0.74
6 Left	0.006	0.21	-0.003	0.71	-0.01	0.64	-0.02	0.11
6 Right	0.006	0.20	-0.004	0.65	-0.01	0.71	-0.02	0.10
4 Left	-0.003	0.42	-0.001	0.93	0.07	0.02	-0.003	0.72
4 Right	-0.004	0.43	-0.001	0.93	0.07	0.02	-0.004	0.66
3 Left	-0.001	0.71	-0.001	0.86	0.04	0.09	-0.009	0.29
3 Right	-0.001	0.81	-0.001	0.90	0.05	0.09	-0.01	0.20

1 - Regression Model: $HL^2 = \beta_1 + \beta_2$ Age + β_3 lnTSty3 + β_4 lnNoise3 + β_5 Cigyr + β_6 RCh + β_7 RN + β_8 Solv

2 - HL based on WORST of pre- or post-shift measure

4.4.2.3 Linear Assumption using 'Best' HL and TWA Exposures

The lifetime noise and, to a lesser extent, styrene exposure estimates for each subject were heavily influenced by the total duration of work and thus, indirectly, by age. The correlation coefficients between age and the lifetime noise exposure and age and lifetime styrene exposure were 0.55 and 0.16, respectively Therefore, this could have resulted in increased variability and an increase in the standard error of the noise and styrene regression coefficients. To explore an alternative analytical approach, the time weighted average (TWA) values of the lifetime noise and styrene exposures were calculated by dividing the cumulative exposure estimates by the total duration of exposure. These TWA exposures, taken as the natural logarithmic transformations for styrene (lnTWA) and for noise (lnTWAN), were used in

the multiple linear regression analysis including age, smoking, recreational chemical and noise and occupational solvent exposures. Considering those subjects less than 50 years of age, age and noise exposure (as lnTWAN) were significant factors in hearing loss (Table 4-26A). Using this TWA approach, the association between noise and hearing loss, at 3 and 4 kHz, appeared stronger than previously (Table 4-19A). Styrene exposure (as lnTWA) only approached significance at 6 kHz in the left ear (p=0.09).

Table 4-26A: Regression Coefficients and Associated p-values for Age, TWA Styrene and TWA Noise Exposures[1] Subjects Age <50 (n=256[2])

HEARING LOSS BY FREQUENCY	Age		lnTWA(sty3)		lnTWA(Noise3)		R^2
	β	p	β	p	β	p	
8 Left	0.57	0.0001	-0.14	0.73	3.13	0.06	0.13
8 Right	0.61	0.0001	-0.28	0.46	3.83	0.02	0.16
6 Left	0.78	0.0001	0.68	0.09	2.23	0.18	0.19
6 Right	0.61	0.0001	-0.12	0.75	3.96	0.01	0.22
4 Left	1.04	0.0001	0.47	0.19	4.54	0.003	0.27
4 Right	0.92	0.0001	-0.34	0.34	5.10	0.0007	0.26
3 Left	0.85	0.0001	0.32	0.28	4.66	0.0002	0.27
3 Right	0.78	0.0001	-0.05	0.87	2.78	0.02	0.23

1 - Regression Model: $HL^3 = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTWA(Sty3) $+ \beta_4$ lnTWA(Noise3) $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

2 - 262 Subjects were less than 50 years of age; however, due to missing data, n=256

3 - HL based on *'best'* of pre- or post-shift measure

Smoking was significant at 6 kHz (right ear) and also approached significance at 6 (left) and 8 kHz (Table 4-26B). Recreational noise was a significant contributor to hearing loss at 6 kHz in the right ear. Similarly recreational chemical and occupational solvent exposures were significant contributors at 4 kHz (left ear) and 6 kHz (left ear), respectively.

Table 4-26B: Regression Coefficients and Associated p-values for Smoking, Recreational Noise & Chemical and Occupational Solvent Exposures[1]
Subjects Age <50 (n=256)

HEARING LOSS BY FREQUENCY	Cigyr		Rec Noise		Rec Chem		Solvent	
	β	p	β	p	β	p	β	p
8 Left	0.008	0.08	-0.005	0.53	-0.02	0.47	-0.74	0.66
8 Right	0.007	0.13	-0.01	0.25	-0.01	0.66	-0.49	0.76
6 Left	0.008	0.10	-0.003	0.71	-0.02	0.53	-3.74	0.03
6 Right	0.010	0.004	-0.02	0.02	-0.01	0.72	-0.79	0.62
4 Left	-0.003	0.94	0.004	0.64	0.06	0.03	-0.98	0.52
4 Right	0.005	0.24	-0.001	0.89	0.009	0.72	0.01	0.99
3 Left	-0.001	0.99	-0.001	0.94	0.03	0.16	-1.51	0.22
3 Right	-0.001	0.94	-0.001	0.98	-0.007	0.74	-1.61	0.19

1 - Regression Model: $HL^2 = \beta_1 + \beta_2$ Age + β_3 lnTWA(Sty3) + β_4 lnTWA(Noise3) + β_5 Cigyr + β_6 RCh + β_7 RN + β_8 Solv

2 - HL based on '*best*' of pre- or post-shift measure

Using the data subset with an exclusion of those subjects with a significant hearing loss (as described in Section 4.4.2.1, page 85), as well as the age exclusion (n=237), age and lnTWA(Noise3) remained as significant variables in the model (Table 4-27A). The TWA styrene exposure (lnTWA) appeared to be a significant contributor to hearing loss, in only the left ear at 6 kHz, with this trend also appearing at 3 and 4 kHz. Smoking approached significance for both the left and right ear at 6 and 8 kHz and recreational noise exposure appeared to affect significantly only the right ear at 6 kHz (Table 2-27B). In addition, hearing loss in the left ear at 3 and 4 kHz appeared to be influenced by recreational chemical exposure, while occupational solvent exposure appeared to affect hearing loss in the left ear at 6 kHz.

Table 4-27A: Regression Coefficients and Associated p-values for Age, TWA Styrene and TWA Noise Exposures[1] Subjects Age <50, HL(3-4,6-8) <50 (n=237[2])

HEARING LOSS BY FREQUENCY	Age		lnTWA(sty2)		lnTWA(Noise3)		R^2
	β	p	β	p	β	p	
8 Left	0.30	0.0090	0.24	0.45	1.76	0.18	0.09
8 Right	0.41	0.0007	0.03	0.92	2.92	0.03	0.13
6 Left	0.55	0.0001	0.90	0.004	1.45	0.27	0.19
6 Right	0.40	0.0004	0.16	0.60	3.10	0.02	0.22
4 Left	0.84	0.0001	0.61	0.05	3.55	0.006	0.27
4 Right	0.73	0.0001	0.10	0.76	4.06	0.002	0.25
3 Left	0.68	0.0001	0.45	0.09	3.88	0.0005	0.26
3 Right	0.61	0.0001	0.23	0.37	2.25	0.04	0.22

1 - Regression Model: $HL^3 = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTWA(Sty3) $+ \beta_4$ lnTWA(Noise3) $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

2 - 243 Subjects were less than 50 years of age and had mean HL<50, however, due to missing data, n=237

3 - HL based on '*best*' of pre- or post-shift measure

Table 4-27B: Regression Coefficients and Associated p-values for Smoking, Recreational Noise & Chemical and Occupational Solvent Exposures[1] Subjects Age <50 HL(3-4,6-8) <50 (n=237)

HEARING LOSS BY FREQUENCY	Cigyr		Rec Noise		Rec Chem		Solvent	
	β	p	β	p	β	p	β	p
8 Left	0.006	0.08	-0.003	0.68	-0.007	0.75	0.73	0.58
8 Right	0.007	0.08	-0.006	.38	-0.002	0.91	-0.58	0.66
6 Left	0.006	0.11	-0.001	0.86	-0.004	0.85	-2.79	0.03
6 Right	0.01	0.0003	-0.02	0.01	-0.001	0.99	-1.20	0.34
4 Left	-0.003	0.41	0.004	0.49	0.07	0.002	-0.03	0.98
4 Right	0.005	0.17	0.002	0.80	0.02	0.41	0.02	0.98
3 Left	-0.001	0.72	-0.001	0.99	0.04	0.05	-0.87	0.43
3 Right	0.001	0.73	0.001	0.92	-0.002	0.91	-1.78	0.09

1 - Regression Model: $HL^2 = \beta_1 + \beta_2$ Age $+ \beta_3$ lnTWA(Sty3) $+ \beta_4$ lnTWA(Noise3) $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

2 - HL based on '*best*' of pre- or post-shift measure

4.4.2.4 Non-Linear assumptions

The logarithmic transformations of the styrene and noise dose variables appear to improve their predictive value for the outcome variable (HL). However, other transformations of these two exposure variables may be more appropriate. To investigate this possibility, a non-linear relationship, in the form of:

$$HL = \beta_0 \text{ Age} + \beta_1 \text{ Sty}^{\alpha 1} + \beta_2 \text{ Noise}^{\alpha 2},$$

was analyzed. An exponent (α) of one indicates no transformation, 0.5 the square root, and close to zero indicates a logarithmic transformation. Based on the linear regression analysis at 8 kHz, first approximations of the slope estimates (β) and exponents (α) were selected as starting values for the SAS NonLinear procedure[141]. The best estimate combinations were determined, for subjects of age<50.(Table 4-28) Using these combinations, estimates were then obtained for 4, 6 and 8 kHz. For noise, the exponents at 6 and 8 kHz were both approximately 0.5, with slopes in the order of 20. However, at 4 kHz the exponent was 1.0 with a slope of 63. The slope estimates for styrene at 6 and 8 kHz were small. At 4 kHz, although the slope estimate was larger (-11.65) and negative, suggesting a protective effect, the exponent was essentially zero (Table 4-28). The multiple regression analysis, for 4, 6 and 8 kHz, was rerun using the determined exponents for styrene and noise dose. The findings were essentially similar to those for the model assuming a linear relationships (Table 4-19A,B), with age and noise exposures being the only

consistently important contributors to hearing loss.

Table 4-28: Non-Linear Estimates for Slopes and Exponents (Age < 50)					
$HL = \beta_0 AGE + \beta_1 Sty^{\alpha 1} + \beta_2 Noise^{\alpha 2}$					
Frequency[a] (kHz)	PARAMETERS				
	β_0	β_1	β_2	$\alpha 1$	$\alpha 2$
8 - 1st approx	0.5	0.05	2.0	0.5	0.5
8 - best estimate	0.49	4×10^{-5}	18.91	0.56	0.51
6	0.56	-0.032	23.40	-1.47[b]	0.56
4	0.70	-11.65	63.22	-0.009	0.95

a - Based on '*best*' hearing loss
b - approximately equivalent to an exponent of 0.6

4.4.2.5 Percentage Working Lifetime as a Laminator

An alternate means of gauging styrene exposure is to consider, for each subject, the total duration spent as a Laminator (highest styrene exposures), as a fraction of the total lifetime work duration (variable: *%LAM*). For subjects (age < 50), multiple regression analysis was carried out on the full model, using the calculated variable, *%LAM*, as a proxy for styrene exposure (Table 4-29). Age and noise exposure remained, as expected, consistently significant variables throughout all frequencies. The variables for smoking and recreational noise and chemical exposures showed little variation from previous analyses. The *%LAM* variable remains insignificant at the higher frequencies (4, 6 and 8 kHz); however, it appeared to approach significance as a factor in hearing loss at 3 kHz.

Table 4-29: Multiple Regression[1] Using % Lifetime as a Laminator (Age <50) n=256

HEARING LOSS	Age		% LAM		Noise		R^2
	β	p	β	p	β	p	
8 Left	0.52	0.0031	2.69	0.35	1.50	0.22	0.13
8 Right	0.56	0.0007	4.32	0.11	1.44	0.11	0.17
6 Left	0.56	0.0015	-0.75	0.79	2.71	0.03	0.17
6 Right	0.43	0.0093	1.06	0.69	2.56	0.03	0.22
4 Left	0.82	0.0001	3.07	0.23	3.25	0.004	0.25
4 Right	0.74	0.0001	2.90	0.25	2.36	0.03	0.25
3 Left	0.64	0.0001	4.07	0.06	2.86	0.002	0.26
3 Right	0.66	0.0001	3.78	0.07	1.13	0.21	0.23

1 - Regression Model: $HL^2 = \beta_1 + \beta_2$ Age $+ \beta_3$ %Lam $+ \beta_4$ lnNoise3 $+ \beta_5$ Cigyr $+ \beta_6$ RCh $+ \beta_7$ RN $+ \beta_8$ Solv

4.4.3 Logistic Regression Analysis

A 2-level discrete response variable (HLf) was created, with the 'f' refering to the actual frequency (HL8, HL6). HLf was assigned a value of "0" for those with *Best* hearing loss, average of left and right ear, greater than or equal to 25 dBHL and conversely a value of "1" for a loss less than 25 dBHL. Using both the age exclusion (Age < 50) and the age and hearing loss exclusion data sets, age continued to be a significant variable for HL at all frequencies (Table 4-30). Noise exposure appeared to be significant, or approached significance as a factor for HL at frequencies of 4 kHz and above. Styrene exposure approached significance (p=0.056) for hearing loss at 6 kHz, when considering the age and hearing loss exclusion data set.

Table 4-30: Probability values for regression coefficients in Logistic Regression analyses with HL defined as ≥ 25 dBHL						
Frequency	AGE		STYRENE		NOISE	
	Age Ex[1]	Age/HL Ex[2]	Age Ex[1]	Age/HL Ex[2]	Age Ex[1]	Age/HL Ex[2]
8	0.02	0.15	0.3	0.6	0.01	0.024
6	0.0000	0.0003	0.14	0.06	0.049	0.08
4	0.0000	0.0005	0.8	0.3	0.002	0.004
3	0.0000	0.0001	0.4	0.12	0.2	0.4

1 - Using Age Exclusion (Age < 50) dataset (n=256)
2 - Using Age and Hearing Loss Exclusion dataset (n=237)

In order to examine whether the selection of 25 dBHL hearing loss as the cutoff point resulted in the loss of important information, the logistic regression analyses were repeated using 20, 30 and 40 dBHL as the cut points. Table 4-31 provides the resultant probability values for each of the variables (age, lnTsty3, and lnNoise3).

Table 4-31: Probability values for regression coefficients in Logistic Regression analyses with HL defined as ≥ λ dB HL (n=256)				
Frequency	λ	AGE	STYRENE	NOISE
8 kHz	20	0.03 [4.6][1]	0.8	0.01 [6.5][1]
8	25	0.02 [5.1]	0.3	0.01 [6.2]
8	30	0.001 [12.3]	0.9	0.04 [4.1]
8	40	0.001 [11.7]	0.6	0.3 [1.0]
6 kHz	20	0.0005 [12.1]	0.1	0.02 [6.1]
6	25	0.0000 [17.7]	0.1	0.05 [3.9]
6	30	0.001 [10.5]	0.9	0.008 [6.9]
6	40	0.0001 [15.2]	0.2	0.02 [5.4]
4 kHz	20	0.0000 [19.4]	0.4	0.004 [8.4]
4	25	0.0000 [19.2]	0.8	0.002 [9.4]
4	30	0.0000 [20.2]	0.4	0.01 [6.4]
4	40	0.0001 [15.9]	0.6	0.08 [3.1]

1 - χ^2 value associated with analysis of maximum likelihood estimates

The relationship between age and hearing loss was sufficiently strong that the

conclusions were unaffected by the cut point (λ) selection. For styrene exposure, the lack of an observed effect was consistent, with styrene exposure only approaching significance at 6 kHz, using λ of 20 or 25 dBHL. The relationship between noise exposure and hearing loss at 4 kHz was also sufficiently pronounced that it can be observed with any cut point 30 dBHL or lower. The effects at 6 and 8 kHz only approach significance at the lower cut points.

4.4.4 Slope Analysis

Depending upon the cause of hearing loss, as discussed in Chapter 2, audiogram patterns vary with frequency. Hearing loss associated with aging occurs initially in the higher frequencies, increasing in magnitude and spreading into lower frequencies with advancing age. Typically the pattern is such that hearing loss at 8 kHz is greater than at 6 kHz, which in turn is greater than at 4 kHz (Figure 2-1, page 35). Noise induced hearing loss (NIHL) initially affects hearing around 4 kHz, causing a greater loss (dip) in this region, with an improvement in hearing at 6 and 8 kHz (Figure 2-2, page 36). The postulated hearing loss attributed to styrene appears to affect predominantly the higher frequencies: 8 kHz and above according to the study by Muijser.[2] Multiple regression analysis was used to examine the relationships between the slopes of the audiogram curves at 3-4, 4-6 and 6-8 kHz. Considering all subjects ($n=298$) as well as those less than 50 years of

age, the slope between 3 and 4 kHz (right ear) approached significance, positively correlated with noise exposure, consistent with the 4 kHz dip (Table 4-32i,ii). For the right ear (using the Age<50 results), the standard error of the parameter estimate (β =1.78) was approximately 50 percent of the estimate, while for the left ear the standard error was approximately 290 percent of the estimate. Therefore, it is possible that a similar association is not seen for the left ear, due to greater variability in the left ear data. In addition, there appeared to be a significant negative relationship between the slope 6-8 kHz (left ear) and styrene exposure, suggesting that styrene had a greater effect at 6 kHz than at 8 kHz. The findings were similar if both the age and hearing loss exclusion were applied to the data set (Table 4-32iii).

In order to examine the effect of noise exposures, those subjects (from the full data set) with ln(Noise3) values less than the mean ln(Noise3), -3.0, were discarded and the slopes re-examined (Table 4-32iv). Noise exposure approached significance ($0.060<p<0.097$), in both left and right ears, for slopes 3-4 and 4-6 kHz, positively and negatively, respectively. This is consistent with the 4 kHz dip for early noise induced hearing loss. Styrene exposures had no effect on slopes, while age approached significance in the left ear 3-4 kHz ($p=0.07$) and right ear 6-8 kHz ($p=0.06$), both consistent with increased loss at the higher frequencies with age.

Table 4-32: Multiple Regression Analyses of Slopes of Hearing Loss Curves

DATASET/ FREQUENCY		AGE		STYRENE		NOISE	
		β	p	β	p	β	p
i. All Subjects, n = 298							
4 - 3 kHz	LEFT	0.12	0.1	0.24	0.3	-0.44	0.6
	RIGHT	0.01	0.9	-0.12	0.6	1.75	0.037
6 - 4	LEFT	-0.03	0.5	0.07	0.7	-0.21	0.7
	RIGHT	-0.06	0.2	0.12	0.4	-0.14	0.8
8 - 6	LEFT	0.02	0.9	-0.33	0.02	0.35	0.4
	RIGHT	0.06	0.2	-0.04	0.8	-0.15	0.8
ii. Age < 50 (n=261)							
4 - 3 kHz	LEFT	0.14	0.1	0.12	0.6	0.28	0.7
	RIGHT	0.11	0.3	-0.18	0.5	1.78	0.042
6 - 4	LEFT	-0.03	0.6	0.07	0.6	-0.47	0.4
	RIGHT	-0.07	0.2	0.07	0.6	0.01	0.9
8 - 6	LEFT	-0.09	0.1	-0.38	0.009	0.51	0.3
	RIGHT	-0.04	0.4	-0.10	0.5	-0.02	1.0
iii. Age <50, HL <50 (n=242)							
4 - 3 kHz	LEFT	0.11	0.2	0.14	0.5	0.10	0.9
	RIGHT	0.06	0.5	-0.05	0.8	1.52	0.08
6 - 4	LEFT	-0.06	0.3	0.12	0.4	-0.39	0.4
	RIGHT	-0.09	0.1	-0.01	0.9	0.09	0.8
8 - 6	LEFT	-0.10	0.085	-0.32	0.037	0.42	0.4
	RIGHT	-0.04	0.4	-0.08	0.6	-0.02	1.0
iv. LnNoise3 > Mean All Subjects							
4 - 3 kHz	LEFT	0.22	0.070	0.34	0.5	3.76	0.08
	RIGHT	-0.11	0.4	0.59	0.3	3.86	0.096
6 - 4	LEFT	0.06	0.5	-0.06	0.9	-2.42	0.08
	RIGHT	0.03	0.7	0.06	0.8	-2.40	0.06
8 - 6	LEFT	-0.03	0.6	-0.03	0.9	2.74	0.02
	RIGHT	0.13	0.057	0.11	0.7	-0.30	0.8

4.5 SELF-REPORTED HEARING ACUITY

All subjects were asked the question:

Do you think your hearing is normal?
(Variable = 'OPINH')

Yes /__/ or No /__/

If hearing loss is defined as a loss of 25 dBHL or greater, the subjective questionnaire response can be compared with the HL at each frequency. In this case, the data on lower frequencies (1 and 2 kHz) were included as these fall within the speech range and therefore were likely of importance. According to the Chi Square statistic, there was a strong association between the response and hearing loss at all frequencies above 1 kHz. The sensitivity of the question, the percentage of those reporting hearing loss who had a loss, ranged from 31 to 43 percent. The specificity, or the true negative rate, ranged from 80 to 87 percent (Table 4-33).

Table 4-33: Relationship Between Self-Reported Hearing Acuity (OPINH) and Measured Loss

Frequency	Chi Square Probability[1]	Sensitivity[2]	Specificity[3]
8	0.000	36%	86%
6	0.000	31%	86%
4	0.000	42%	87%
3	0.000	43%	83%
2	0.039	43%	80%
1	0.023	46%	80%

1 - Chi Square Statistics
2 - % with hearing loss reporting hearing loss
3 - % with no hearing loss reporting no hearing loss

These associations between hearing loss and the response to the above question

(OPINH) were confirmed using logistic regression analyses between the probability of responding positively to the question *(OPINH)* and hearing loss. At each frequency, the slope estimates were similar (0.03 to 0.04) and the relationship highly significant.

The subjects (Age<50) can be categorized, at each frequency, as having a hearing loss less than 20 dBHL, between 20 and 40 dBHL, or greater than 40 dBHL; corresponding to essentially normal, moderate loss and substantial loss, respectively. Table 4-34 provides the proportion of subjects, in each hearing loss category, who were of the opinion that their hearing was NOT normal (ie. '*OPINH*' = No). Generally, around 40 percent of those with a substantial hearing loss recognized their handicap, while 10 to 15 percent of those with essentially normal hearing believed they had some abnormality.

Table 4-34: Proportion of Subjects[1] with given HL reporting hearing abnormality (n= 262)

Frequency/Ear	HL < 20 dB	20 ≤ HL < 40	HL ≥ 40 dB
8 kHz Left	13% [150]	26% [77]	40% [35]
6 kHz Left	11% [82]	17% [123]	42% [57]
4 kHz Left	13% [171]	26% [53]	45% [38]
3 kHz Left	14% [186]	35% [52]	38% [24]
2 kHz Left	18% [227]	30% [30]	60% [5]
1 kHz Left	18% [235]	45% [22]	40% [5]

1 - [# subjects in category]

Table 4-34 also demonstrates clearly the variation in hearing loss with frequency. Over 86 percent of all subjects (age<50) had essentially normal hearing at 1 and 2 kHz, while at 6 and 8 kHz many more subjects

demonstrated hearing losses.

Subjects were asked to rate the difficulty they have in hearing in certain everyday situations, ranked in five categories from never to always (Appendix II, page 168). Using the same definition of hearing loss, 25 dBHL or greater, and the five category ranking, chi squared statistics for trends demonstrated that there were significant associations between some of the questions and measured hearing loss (Table 4-35).

Table 4-35: Relationship Between Response to Selected Situations and Measured Loss Loss

QUESTION	FREQUENCY					
	8	6	4	3	2	1
Diff hearing one person[1]	0.021	0.07	0.009	0.016	1.0	0.8
Sens.[2]	25%	22%	26%	29%	17%	20%
Sp.[3]	87%	87%	87%	86%	84%	84%
Diff hearing in Groups	0.001	0.00	0.000	0.000	0.003	0.04
Sens.	38%	36%	44%	51%	58%	50%
Sp.	82%	84%	84%	82%	60%	78%
Difficulty at Work	0.3	0.3	0.3	0.004	0.2	0.5
Sens.	46%	45%	46%	61%	58%	50%
Sp.	61%	61%	61%	63%	60%	40%
Difficulty with TV	0.021	0.1	0.042	0.1	0.6	0.2
Sens.	42%	36%	41%	41%	25%	50%
Sp.	73%	72%	72%	71%	69%	30%
Difficulty with Doorbell	0.1	0.1	0.05	0.031	0.018	0.01
Sens.	7%	6%	8%	2%	17%	20%
Sp.	97%	97%	97%	97%	97%	97%
People speak clearly	0.5	0.1	0.1	0.013	0.2	0.1
Sens.	22%	25%	27%	34%	33%	40%
Sp.	81%	83%	82%	83%	81%	81%
Buzzing/Ringing in ears	0.6	0.3	0.3	0.6	0.4	0.3
Sens.	33%	41%	41%	39%	25%	20%
Sp.	63%	66%	66%	65%	64%	64%

1 - p-value associated with χ^2 test for trends, for the response to each question (see Appendix II, page 168) and hearing loss

2 - sens = sensitivity: % with HL>25 dB reporting difficulty

3 - sp = specificity: % with HL<25 dB reporting no difficulty

The 5 category ranking for responses to the questions was collapsed into two levels: never/ever. The chi square statistics yield similar results; however, this also allowed examination of the sensitivity and specificity of the questions (Table 4-35). As was the case for self-reported hearing acuity, sensitivity values were low, particularly for the variables regarding difficulty hearing the doorbell, when only one person is speaking and whether people speak clearly. The variables relating to difficulty hearing in groups, at work and the TV had the highest sensitivity values, 36 to 61 percent, depending upon frequency.

Figure 4−1: Age Distribution (n=299)

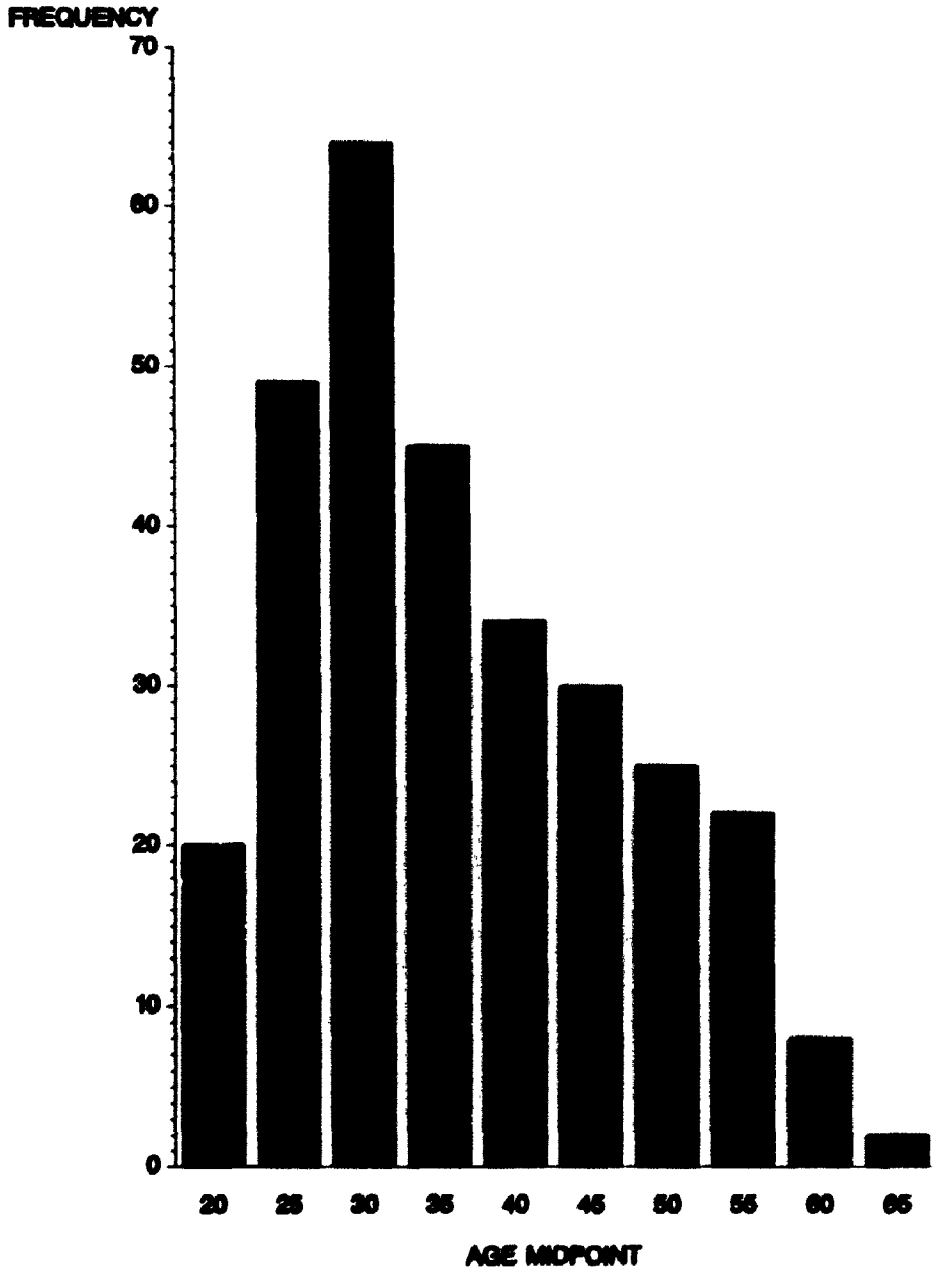


Figure 4−2: Measured TWA Styrene Exposure

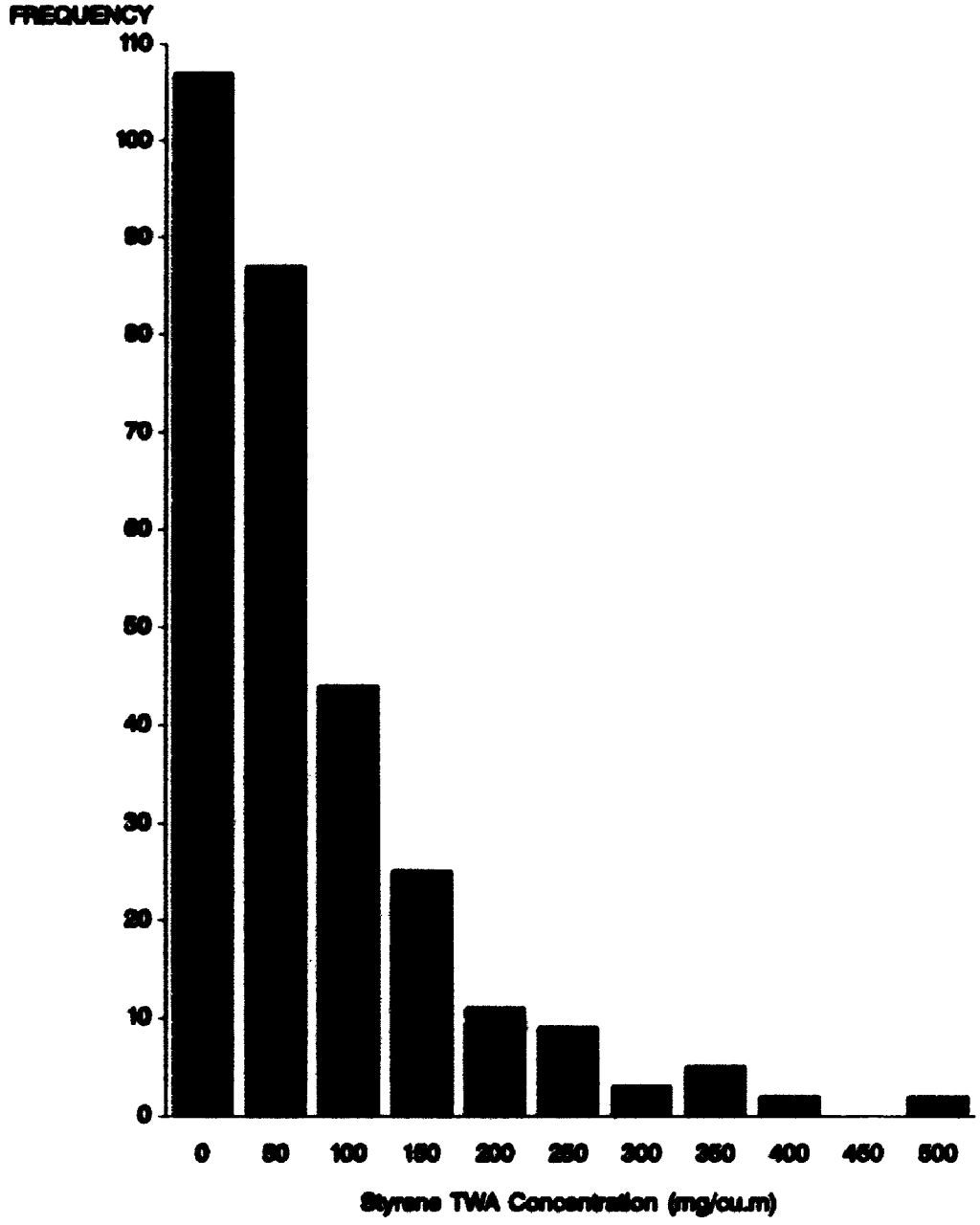


Figure 4−3: Measured Noise Exposure

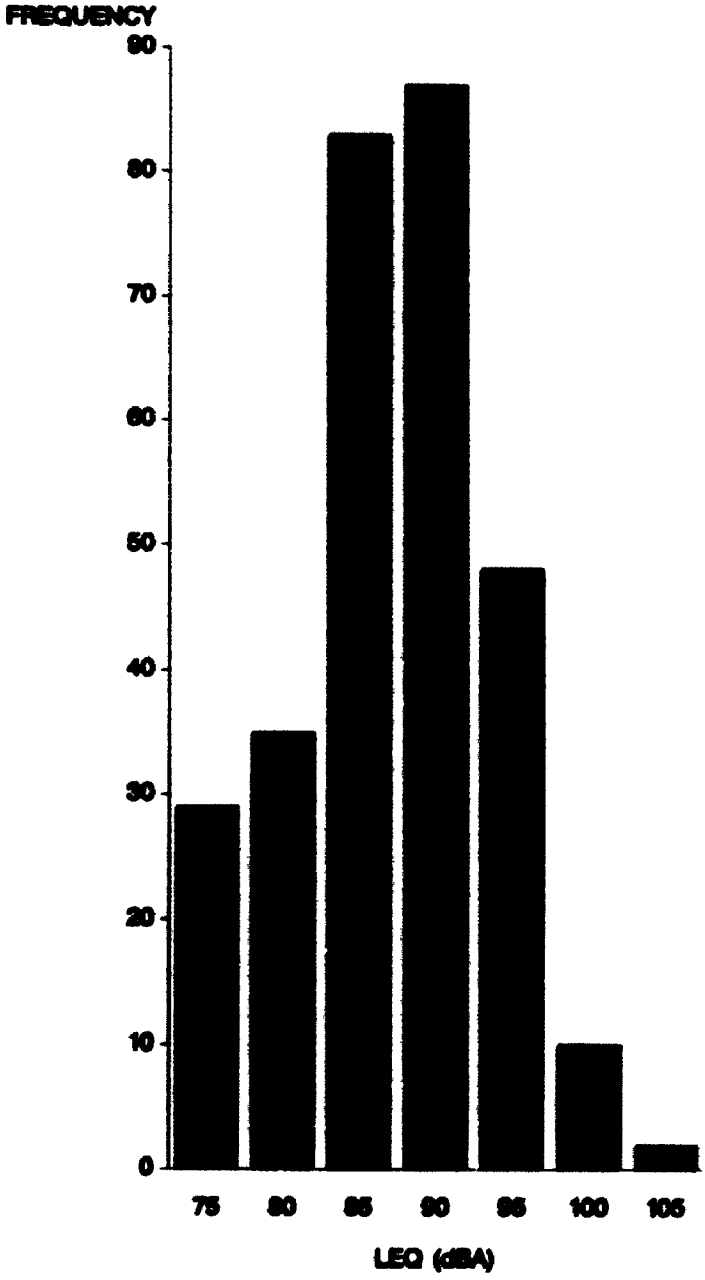


Figure 4–4: Hearing Loss Change Over Shift
Left Ear 4 kHz

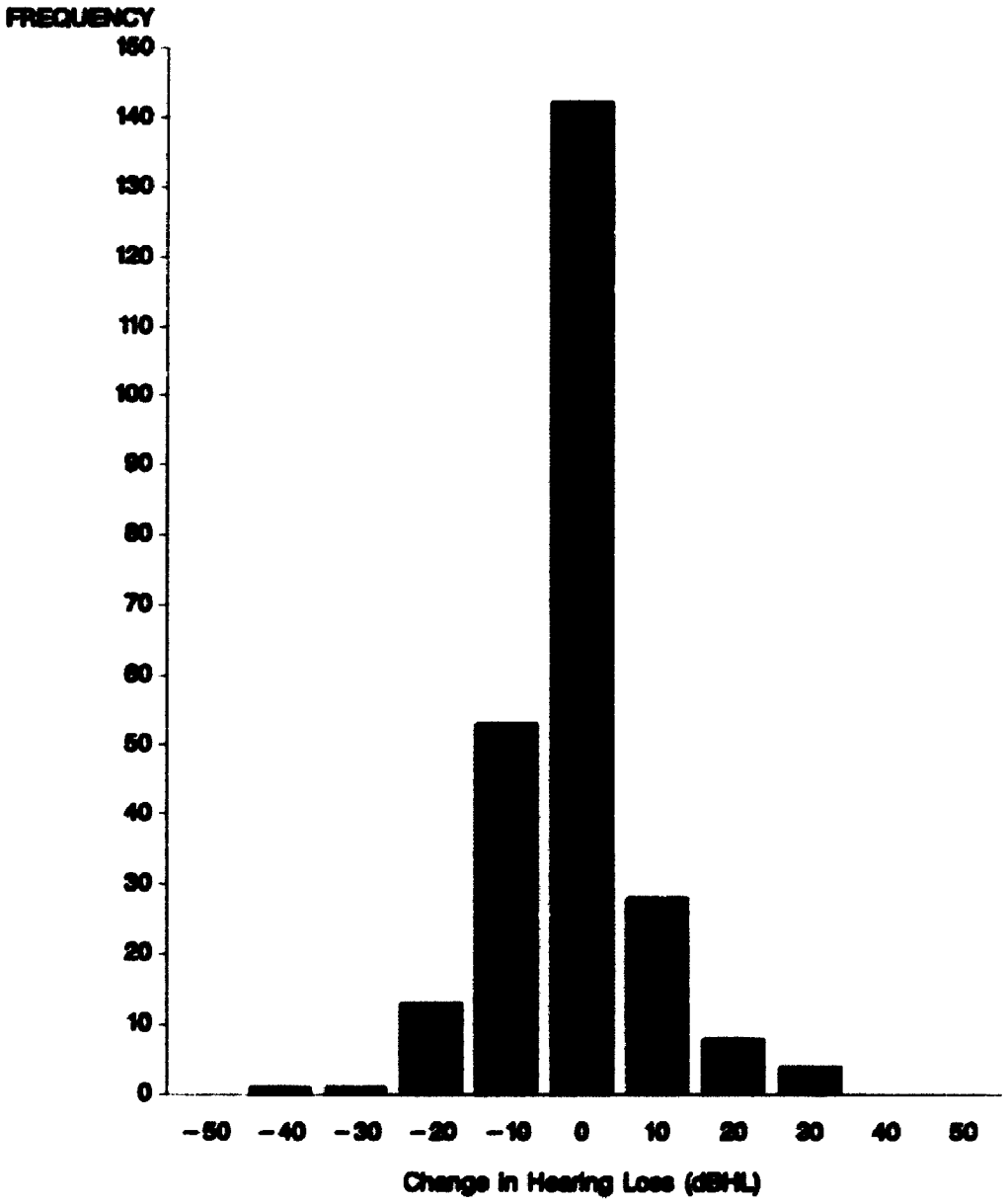


Figure 4–5: Hearing Loss (Best, 4 kHz)
Left Ear – All Subjects

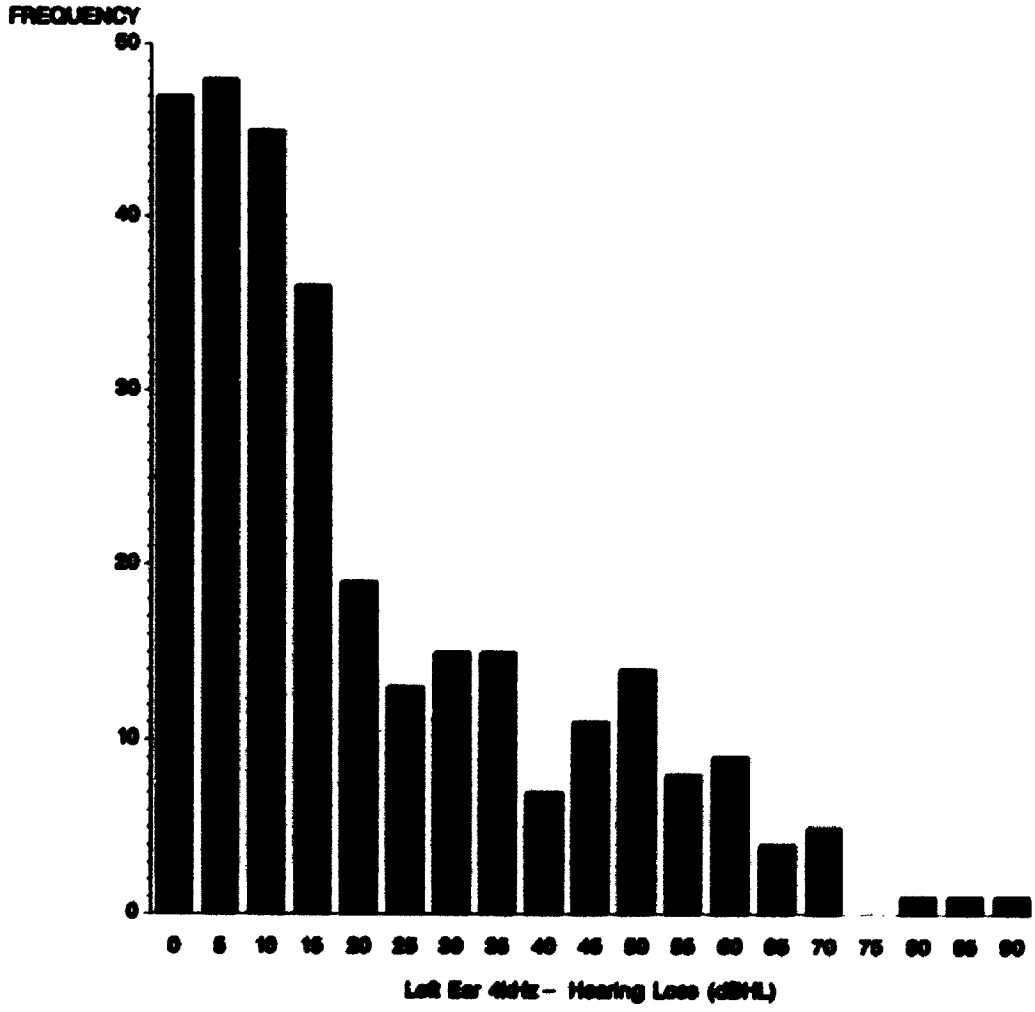


Figure 4–6: Hearing Loss (Best, 6 kHz)

Left Ear – All Subjects

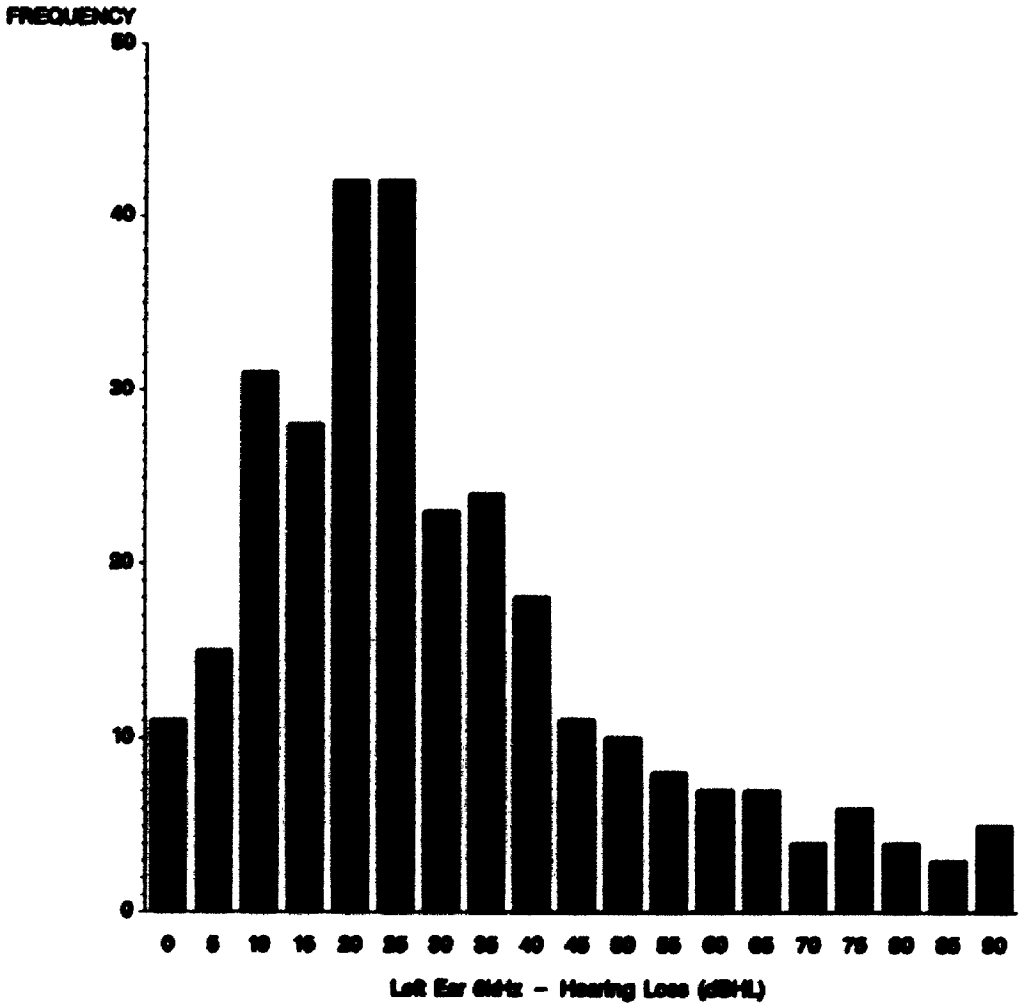


Figure 4–7: Hearing Loss (Best, 8 kHz)
Left Ear – All Subjects

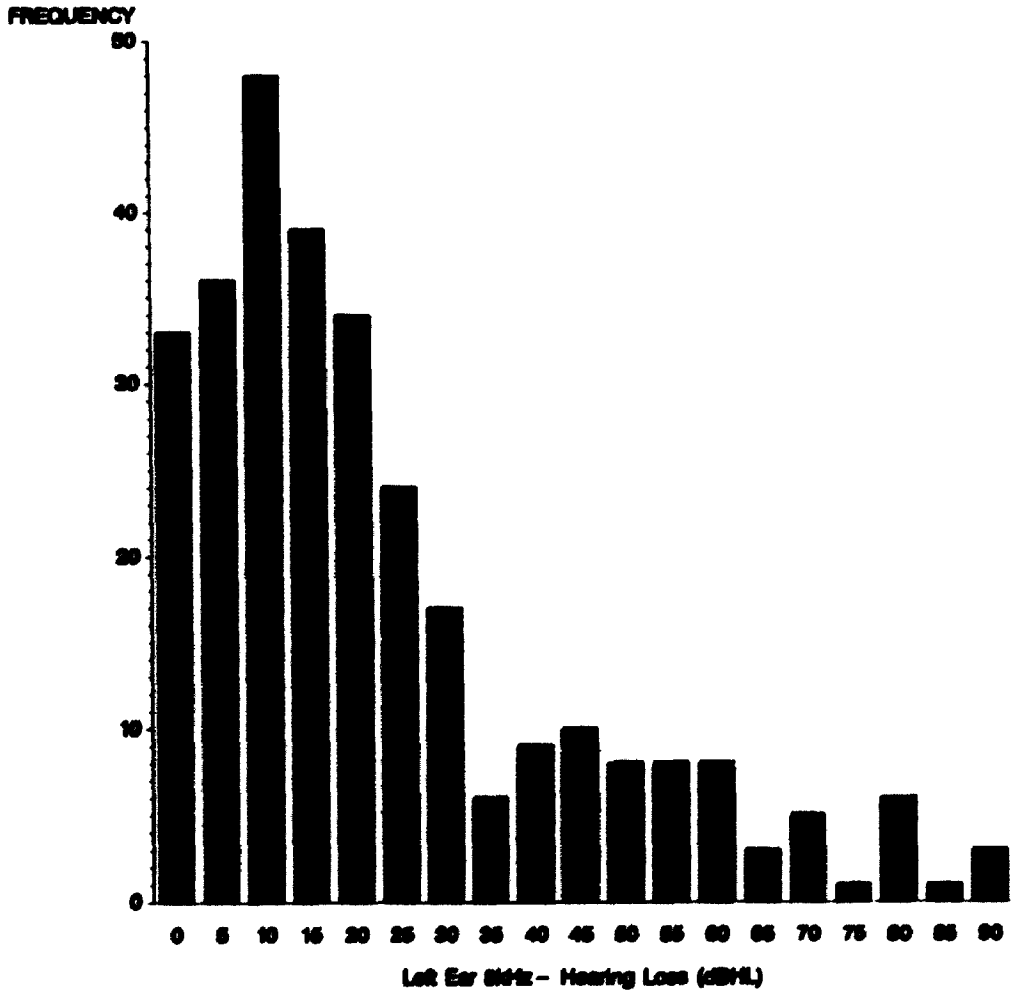
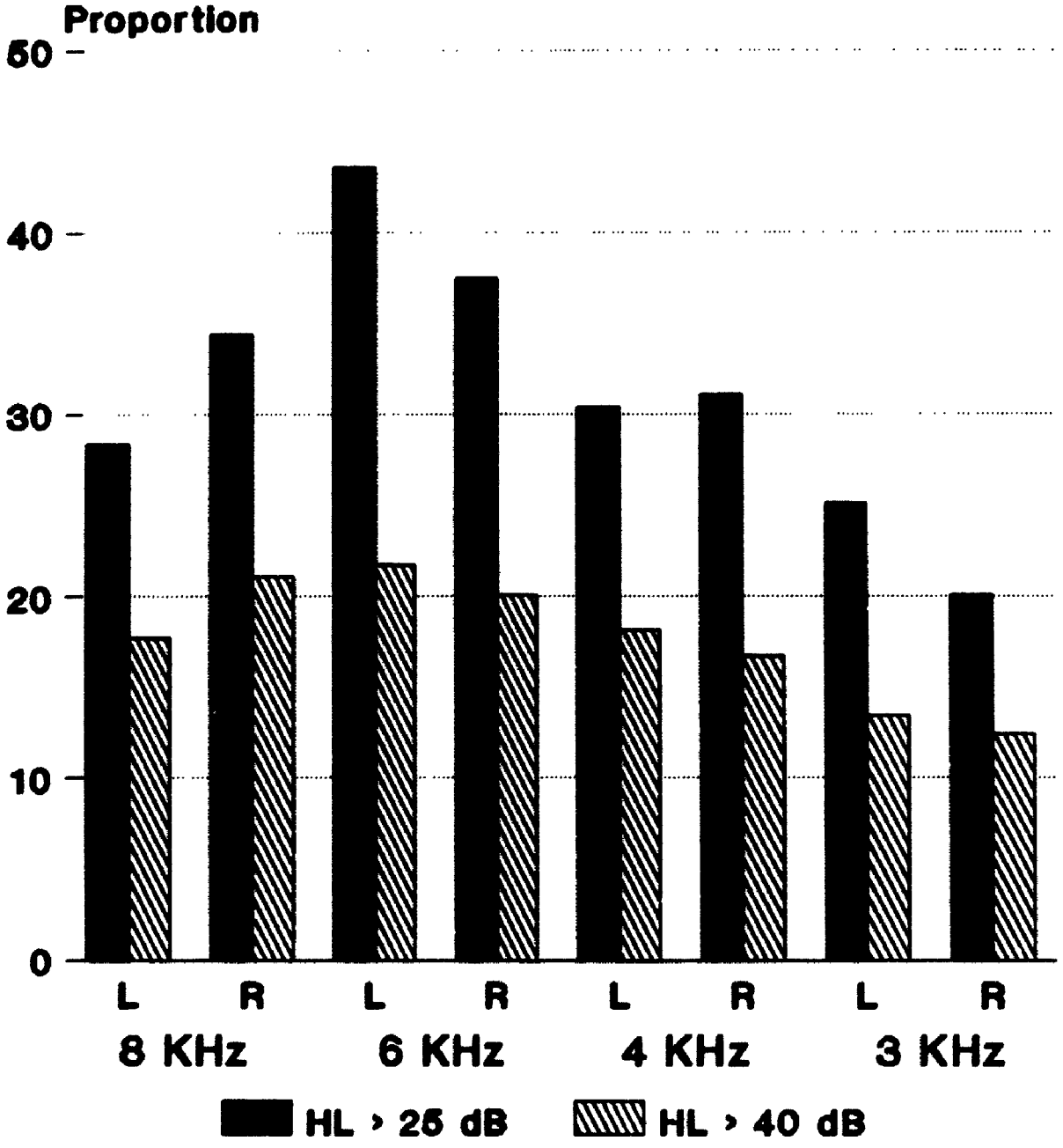


Figure 4-8: Proportion of Subjects With Hearing Loss



Based on 'Best' hearing

Figure 4–9: Geometric Mean Hearing Loss By Age Group

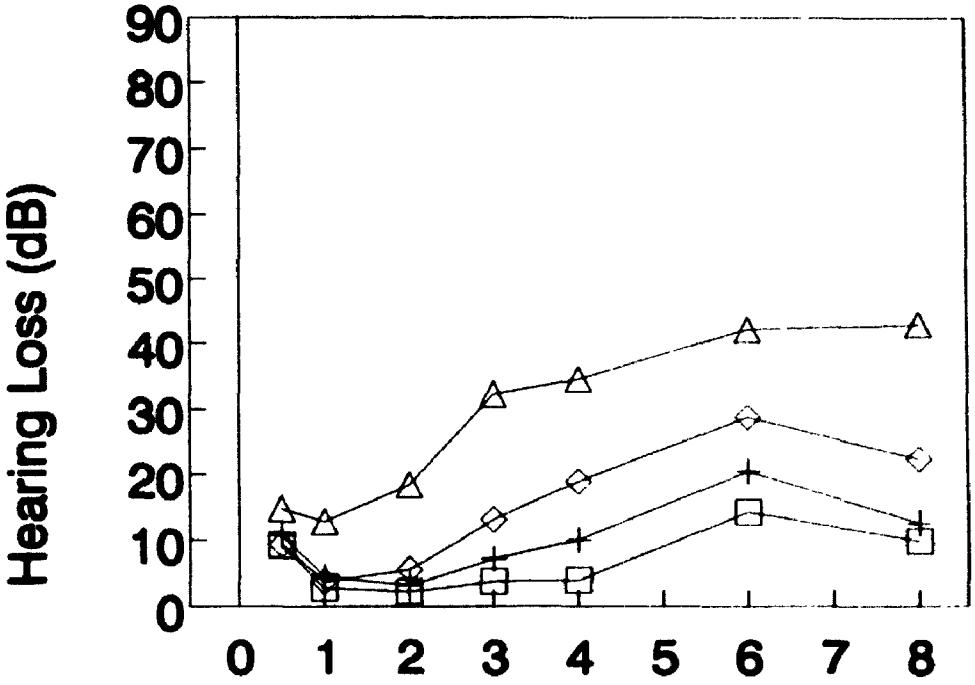


Figure 4–10A: Styrene Lifetime Exposure Age < 50

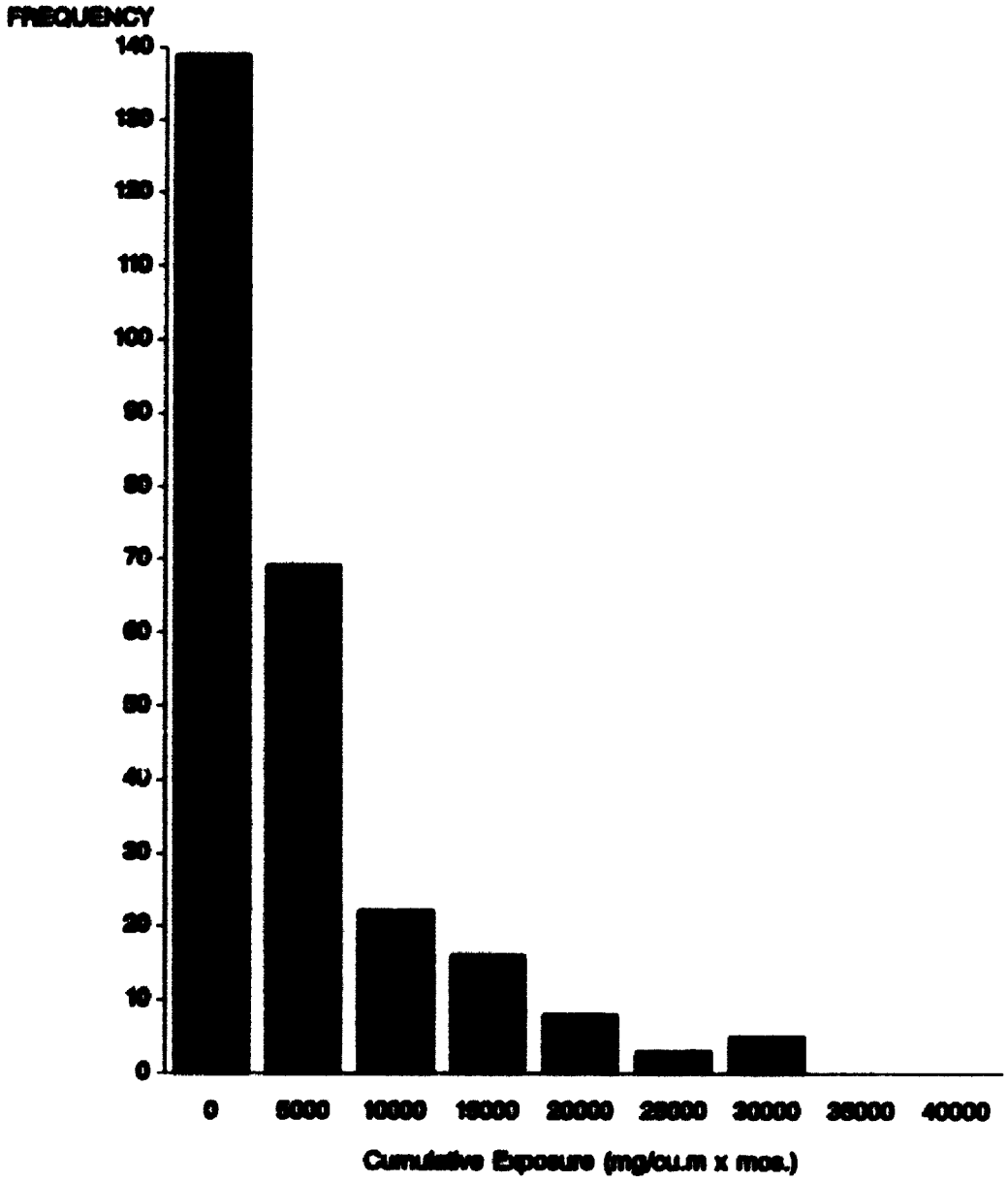


Figure 4–10B: Log Transformation of Styrene Lifetime Exposure – Age < 50

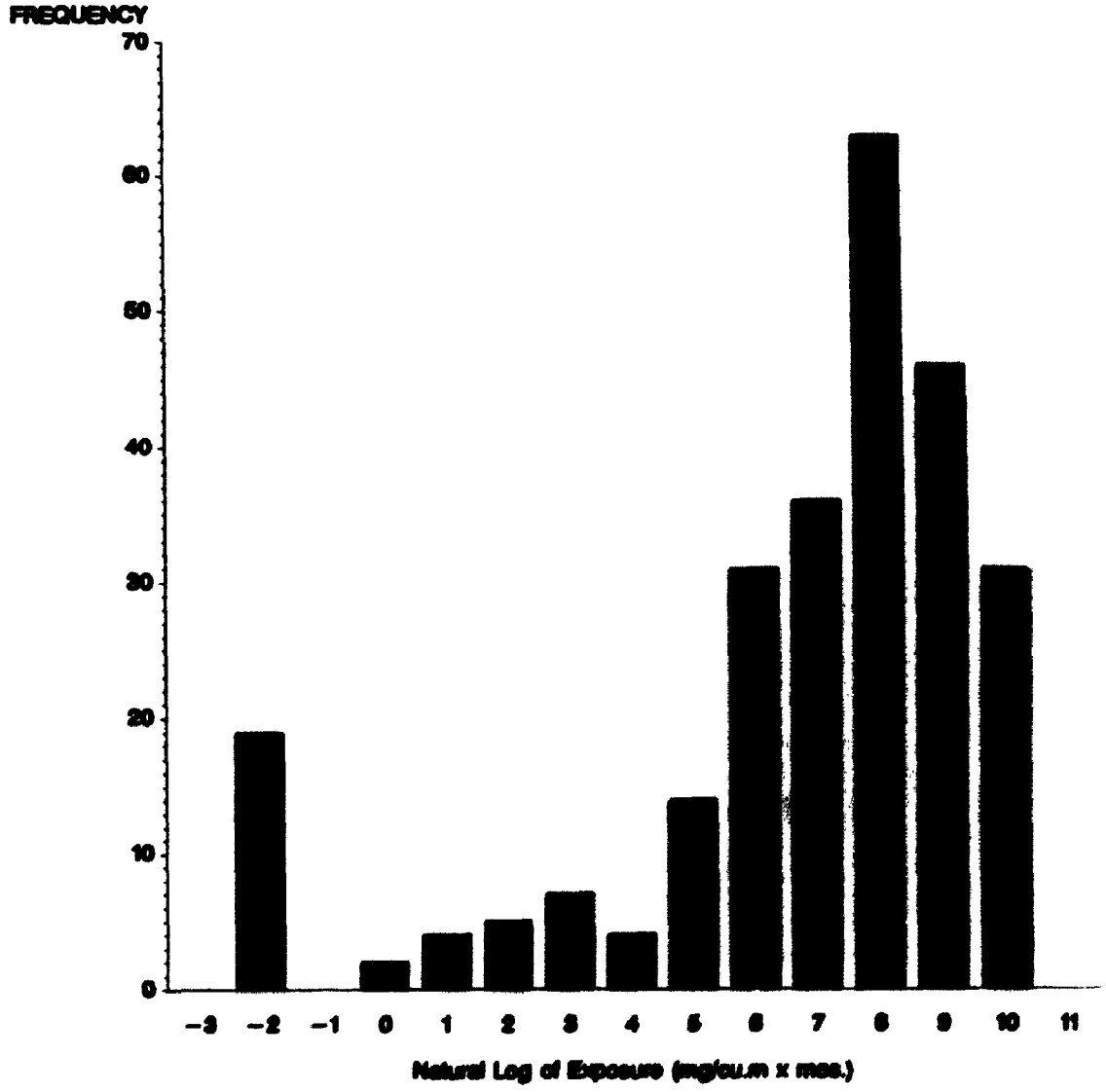


Figure 4–11A: Noise Lifetime Exposure Age < 50

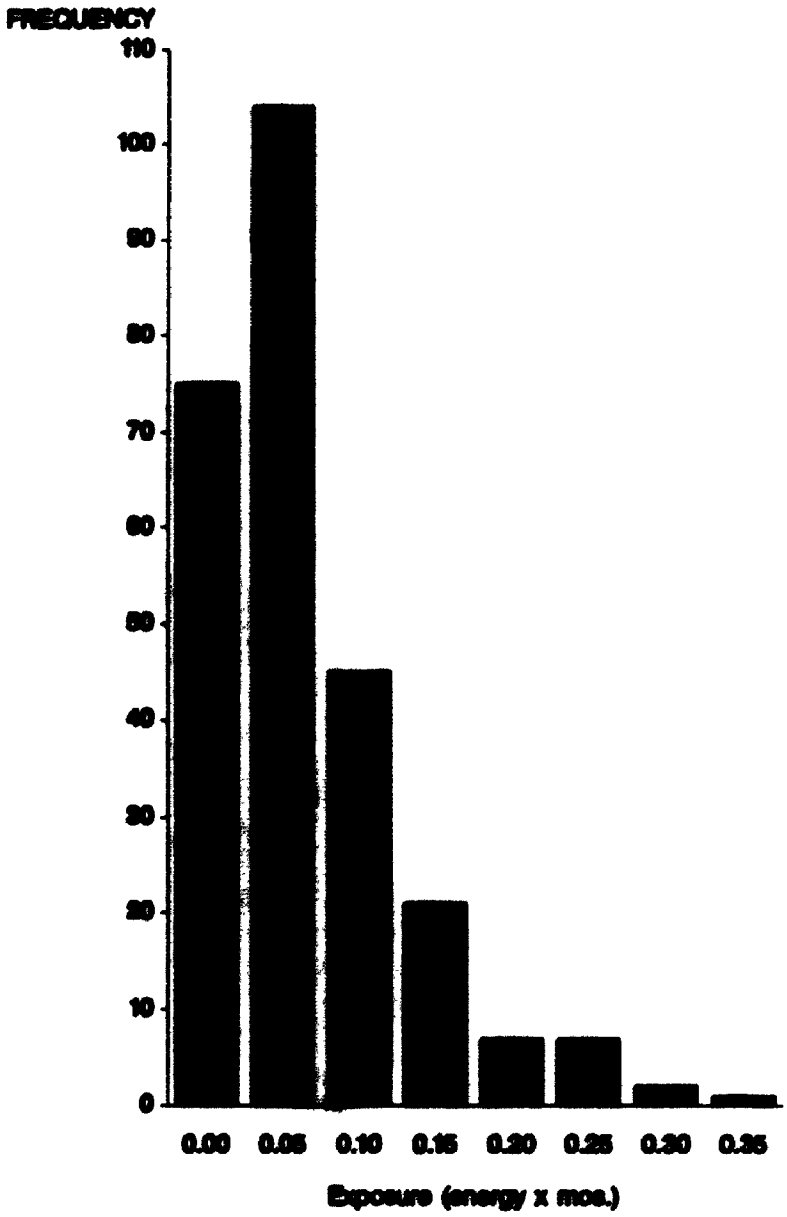


Figure 4–11B: Log Transformation of Noise Lifetime Exposure – Age < 50

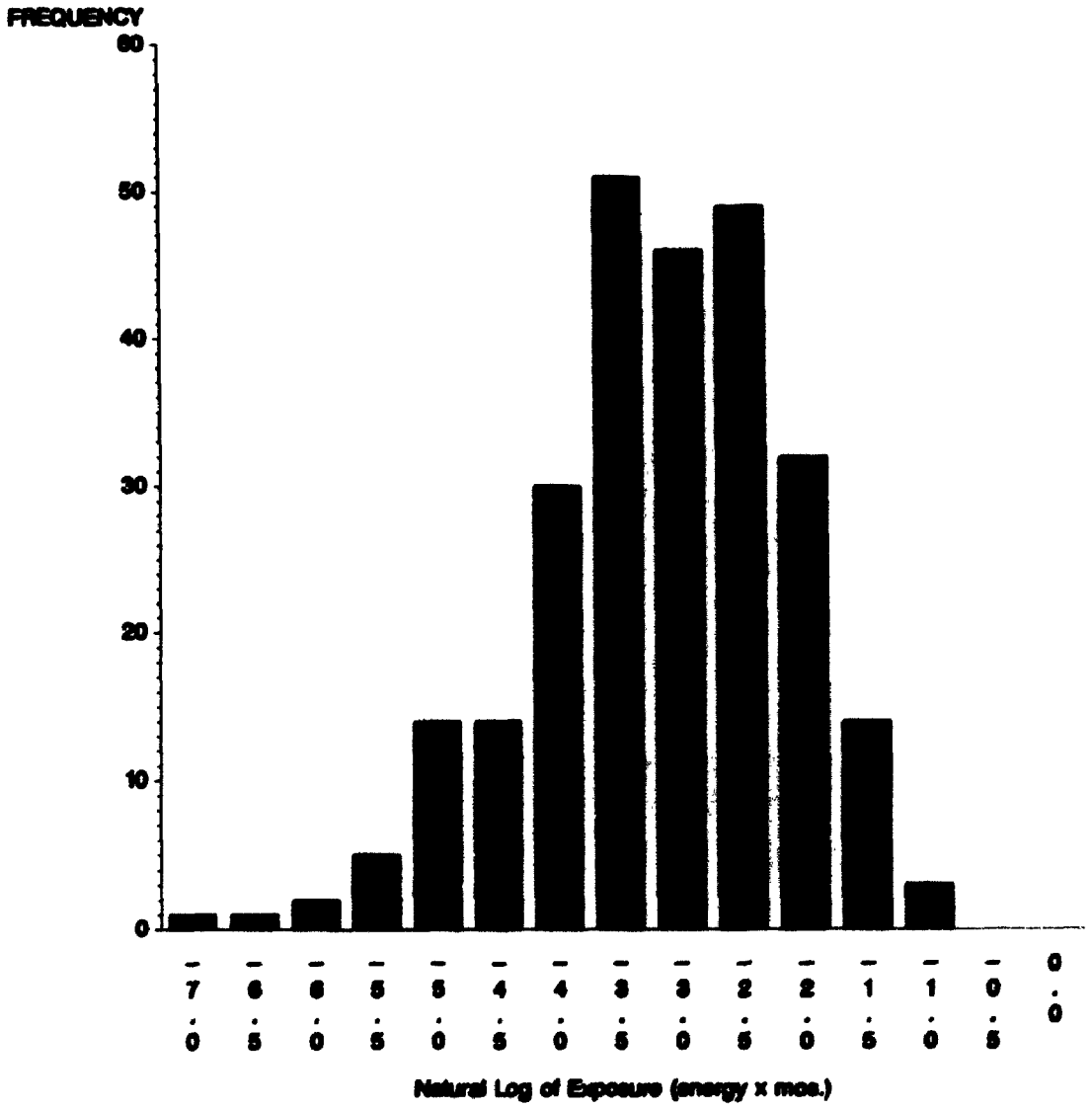


Figure 4–12: Cigarette Smoking (Variable = Cigyr)

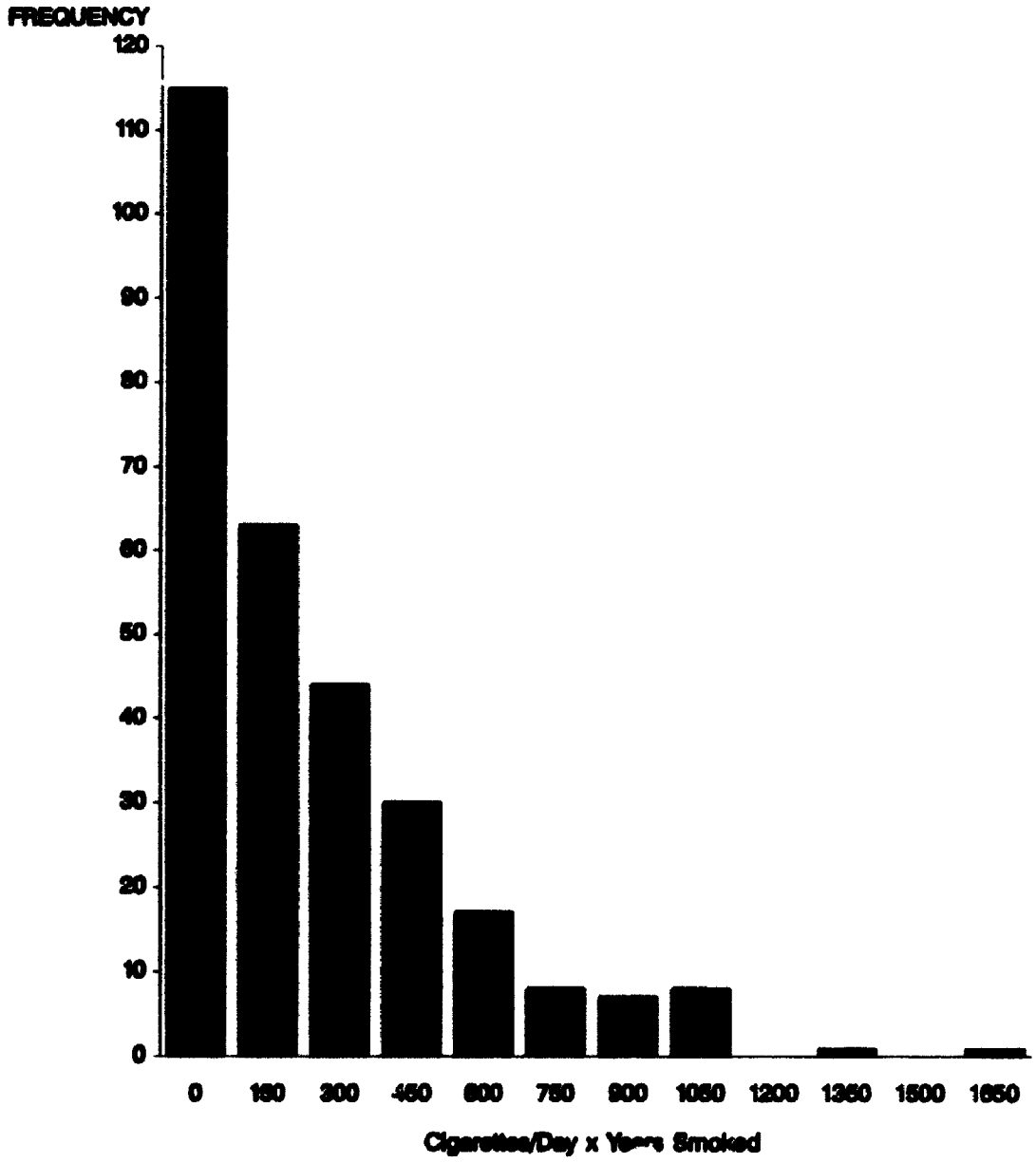


Figure 4–13: Recreational Chemical Exposure (Variable = RCh)

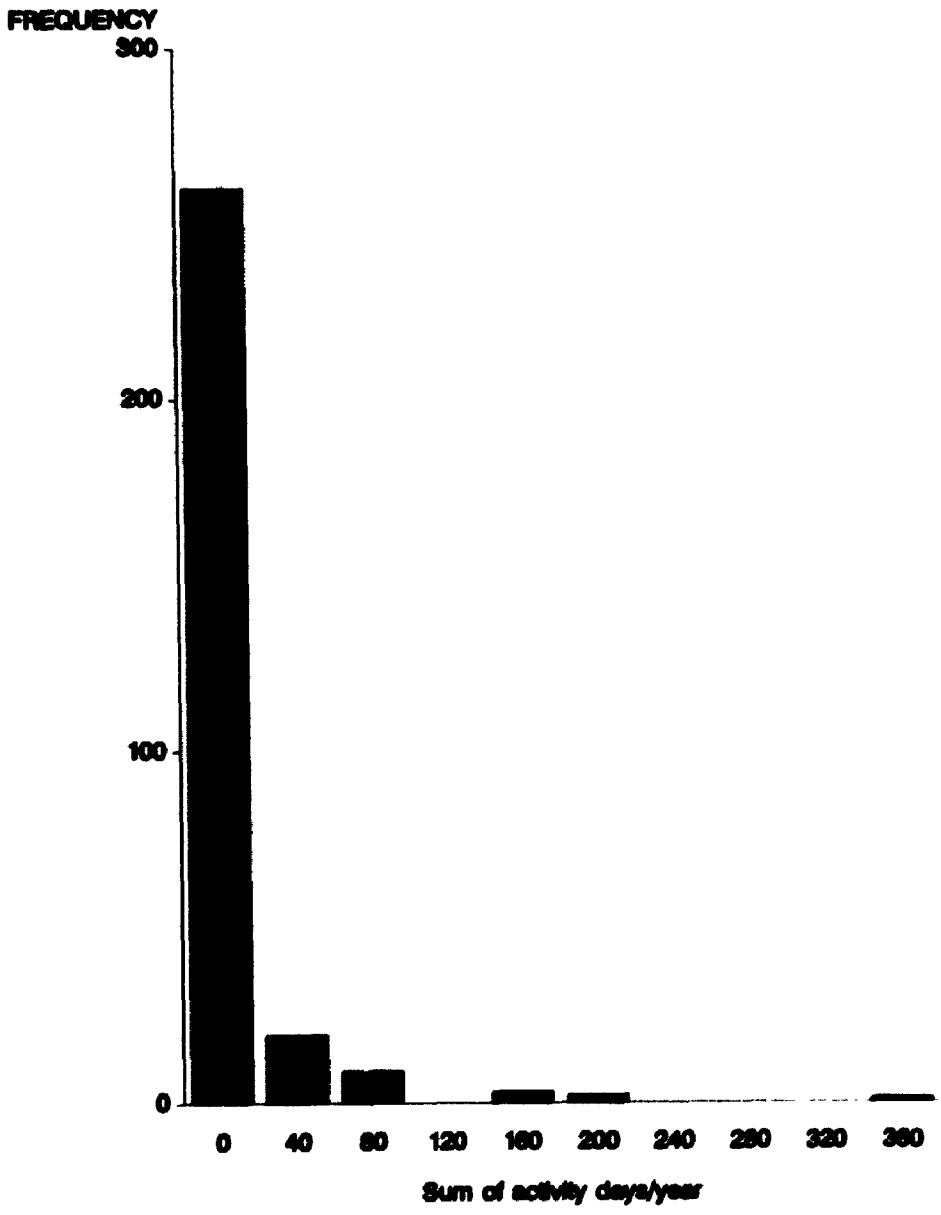


Figure 4−14: Recreational Noise Exposure (Variable = RN)

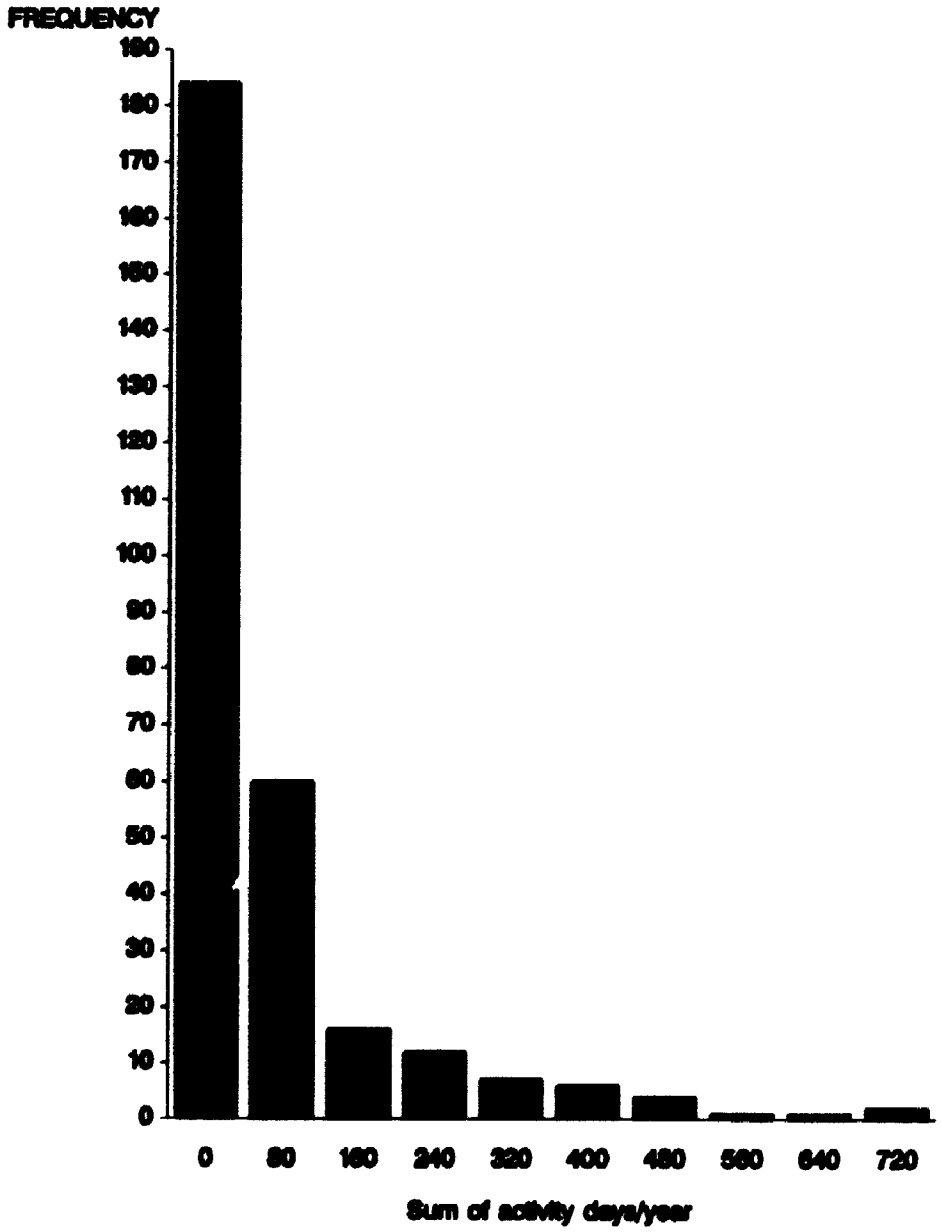
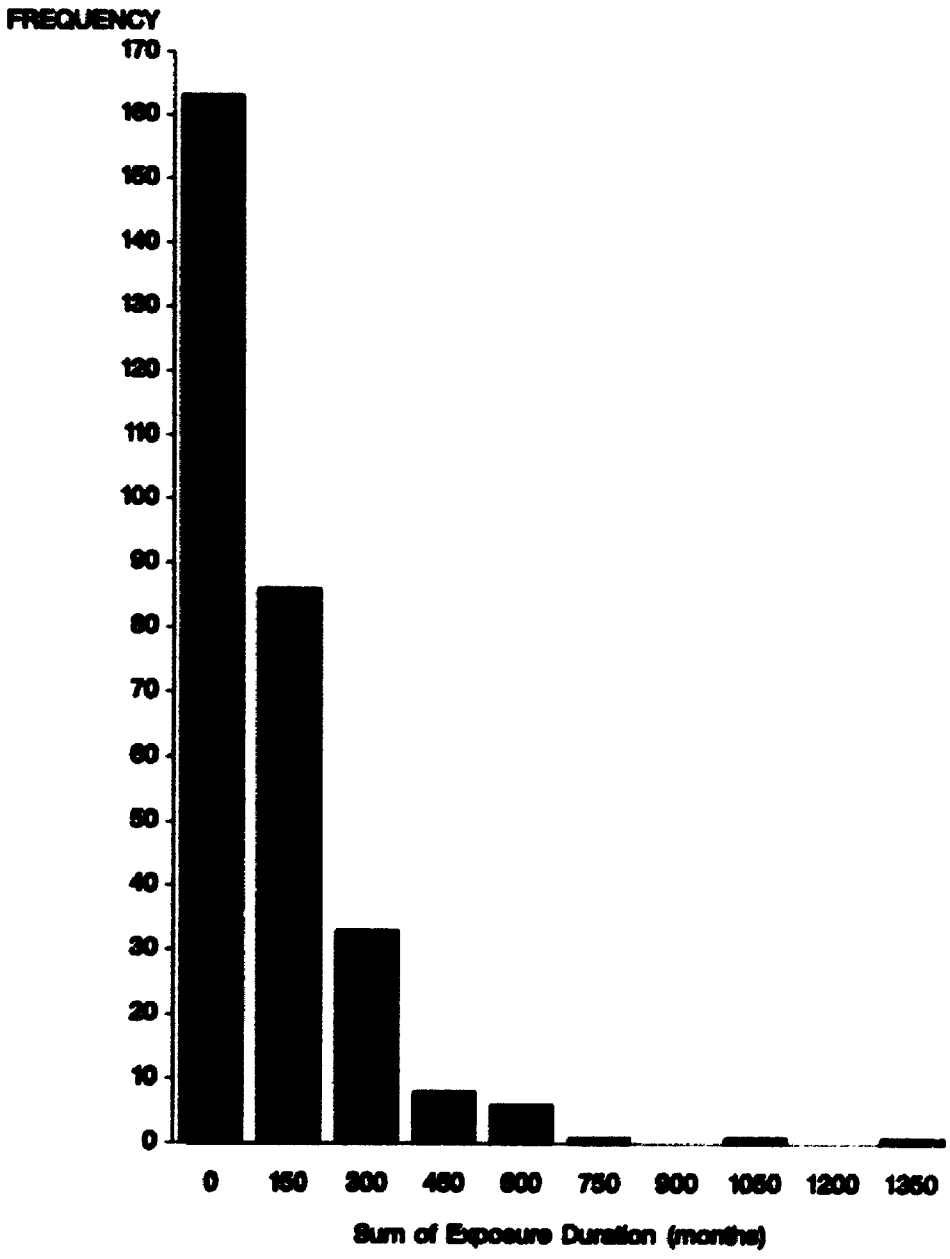


Figure 4–15: Other Occupational Solvent Exposures (Variable = Solv)



CHAPTER 5: DISCUSSION

5.1 Current Exposures to Styrene and Noise

The time-weighted average exposure guideline for styrene, recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 213 mg/m^3 (50 ppm).[133] This value has been set to prevent the usual narcosis and irritation caused by aromatic hydrocarbons, as well as at one tenth of the lowest concentration possibly causing lymphoid or haematopoietic tumours in female rats.[143] In Nova Scotia, exposure standards are based on these ACGIH values. This is also identical to the current Ontario time-weighted average exposure criterion (TWAEC) specified by the "*Regulation Respecting Control of Exposure to Biological or Chemical Agents - made under the Occupational Health & Safety Act*" (Ontario Regulation 654/86). This regulation also stipulates a special exemption for workplaces using styrene-based polyester resins in conjunction with a fibrous reinforcing agent (s.9, OR 654/86). In these workplaces, TWA exposures may go as high as 426 mg/m^3 (100 ppm), although respiratory protection is to be provided and worn for exposures between 50 and 100 ppm. However, in August 1992, a notice of proposed change to 101 occupational exposure limits was published in the *Ontario Gazette*. The proposed styrene exposure limit, based on the current Swedish standard, was given as 85 mg/m^3 (20 ppm), with no mention of exemptions. It is apparent, from Table 4-1, that the plants had geometric mean TWA exposures within the current standard, with the exception of two small (n=9 & 2 employees) Nova Scotia plants. Most of the plants, however, may have difficulty in meeting the newly proposed Ontario standard of 85 mg/m^3.

The mean styrene exposure for laminators (arithmetic mean: 108.7 mg/m^3, geometric mean: 58.6 mg/m^3, Table 4-4) was found to be lower than those previously reported in the literature. Crandall, in 1981, reported arithmetic mean exposures of 287 and 330 mg/m^3 for hull and deck laminators and 187 mg/m^3 for small part laminators, in the boat building industry.[144] In the same industry, arithmetic mean exposures for laminators have been reported as ranging from 166 mg/m^3 (SD=106, n=23) to 865 mg/m^3 (SD=507, n=94). Geometric mean exposures in boat building laminators have been reported at 350[145], 331 and 313[146] mg/m^3. More recently (1992) in the Netherlands, lower exposures have been reported, with geometric mean exposures during hand and spray layup of large surfaces from 97 to 212 mg/m^3, and 50 to 135 mg/m^3 for small parts.[147] The exposures of the laminators in the current study fall just within this latter range for small part laminators.

Exposures to contaminants in the workplace generally decrease over time as a result of increased knowledge and concern regarding workplace health hazards, the lowering of exposure standards and the improvement of engineering and other forms of control. This has been demonstrated for styrene exposure in the Netherlands over the period 1955 to 1988.[148] Thus the lower exposures found in the current study, as compared to the earlier studies, was to be expected. In addition, in the studies cited above, boat building operations have been demonstrated to be associated with the higher styrene exposures. Due to the decline in the Canadian economy, fewer fibreglass boat building enterprises were found in Southern Ontario and Nova Scotia than expected,

likely also an important contributing factor in the lower exposures. As a consequence of the relatively low exposures, the vast majority of subjects (70 percent) never used respiratory protection and only 6 percent of all subjects reported using this type of protective device more than 50 percent of the time.

In Ontario, noise exposure standards are found in the *Industrial Establishments Regulation made under the Occupational Health and Safety Act* (Ontario Regulation 658/79 as amended by OR 844/79). This current legislation specifies a maximum 8 hour exposure of 90 dB(A), with a 5 dB exchange rate. In addition to debate, as discussed in Section 3.7, regarding the choice of a 3 or 5 dB exchange rate, there is also a lack of consensus on the appropriateness of selecting 90 dB(A) as an acceptable exposure for 8 hours. Other jurisdictions, including the province of Nova Scotia, and the American Conference of Governmental Industrial Hygienists[133], have specified 85 dB(A) as the maximum permissible exposure for an 8 hour period, using a 5 dB exchange rate.

In the present study (Table 4-1), plant arithmetic mean L_{eq} exposures (equivalent continuous exposure, assuming a 3 dB exchange rate) were generally between 85 and 90 dB(A), with only one small plant with 5 employees in Nova Scotia having a mean plant L_{eq} in excess of 90 dB(A). However, individually, 100 of the 299 subjects had full shift noise exposures in excess of 90 dB(A). Assuming a working lifetime of such exposures, these subjects are at increased risk for noise induced hearing loss. As

degree of variability in both sets of hearing loss data was substantial, as demonstrated by the standard deviations.

Table 5-1: Hearing Loss in Left Ear reported by Muijser[2] and the current study for Directly Exposed Workers

STUDY	Frequency (kHz)			
	3	4	6	8
Muijser (n=30)	10.5 ± 13.1	14.3 ± 14.0	20.3 ± 17.4	9.1 ± 14.6
Current (n=170)	19.9 ± 17.9	21.7 ± 20.1	31.2 ± 20.1	23.7 ± 20.9
student's t	2.75	1.93	2.79	3.67
probability	<0.01	<0.1	<0.01	<0.001

1. Arithmetic Mean (dBHL) ± SD

The age of the subjects was similar, a mean age of 34.6 (SD=8.7) for Muijser's directly exposed subjects compared with 36.0 (SD=11) in the current study. The mean styrene exposures in the Muijser study were somewhat higher then in the current study (Table 5-2).

Table 5-2: Styrene Exposures Reported by Muijser[2] and by the current study

Study	Directly Exposed	Indirectly Exposed
Muijser	138 ± 76[1]	61 ± 32
Current	109 ± 98	36 ± 49

1. Arithmetic mean (mg/m^3) ± SD

Muijser determined personal exposures for each subject over three consecutive days and took a mean value, while the current study involved only one sampling day for each subject. As a consequence, the variability in the data

measurable TTS might be expected when subjects are exposed to noise levels greater than 80 dB(A) and that the subject ordinarily recovers from TTS within 14 hours.[149] The pre-shift audiometric measurements in this study were not affected by TTS, since subjects were tested at the beginning of their shift and all had a minimum 14 hours away from work prior to the test. However, the post-shift measurement for many subjects may have been affected by TTS, since the audiogram was taken very near to the end of shift, with no rest period. Thus, for those subjects exposed to high noise levels and not wearing hearing protection, it would be expected that hearing acuity would decrease over the shift due to the effects of TTS.

However, it has also been well established that there is an observed improvement in age-adjusted mean hearing levels in industrial noise exposed populations, tested annually.[134] This phenomenon, called the *learning effect*, has also been observed in individuals tested several times over the course of a day.[91] The improved hearing acuity associated with the *learning effect* competes directly with the expected decline in hearing associated with TTS. In this study, no relationship was observed between the direction of the change in hearing acuity, positive or negative, and whether the subjects had taken previous audiometric tests (Table 4-10). In addition, no relationship between noise exposure and changes in hearing acuity over the shift was found (Table 4-11). Thus, this study was unable to demonstrate either *TTS* or *learning effects*. It is possible that the overall magnitude of the effects from these competing factors may have been small and consequently may not have been detected

with the audiometric method used.

The observed significant relationship between pre-shift, or baseline, hearing loss and change in hearing acuity over the shift suggests that individuals with substantial hearing loss will manifest a smaller change in acuity over shift. This could be interpreted as indicating that acute change in hearing acuity was limited because the sensitivity of the auditory mechanism was already compromised by the presence of existing hearing loss. The importance of age (Tables 4-11, 4-12) might be expected, considering the well documented, strong effect of age on hearing, in this case, on the pre-shift hearing loss.

No important relationships were observed with styrene exposure, suggesting that styrene, at the levels encountered in this study, did not exert an acute effect on hearing. It is possible, however, that due to the aforementioned competing factors, a subtle effect could have been missed. To reduce the possible interference of the *learning effect*, subjects should have a series of audiograms taken one day immediately prior to the study day. In addition, on the study day, all the subjects could be tested with hearing protection, reducing the possibility of TTS due to noise exposures. In field studies, however, this may not be feasible as the repeated audiometric tests would cause significant production loss, which would generally be unacceptable to the industry. Further, the hearing protection would only be effective in reducing noise exposures if compliance were absolute.

5.3 Chronic Changes in Hearing

As described in Sections 3.8 and 4.1, for chronic effects the hearing loss outcome variable used most frequently was the '*best*' value in each ear, that is the best of the pre- or post-shift measurement. The hearing loss outcome variable was used directly. Its logarithmic transformation was also considered, although not used for the following reasons. The correlation coefficients (R^2) were slightly higher in regression models in which the outcome variable was hearing loss, than when the logarithmic transformation was used. The R^2 values for the latter regression models were calculated from the antilog of the predicted outcome variable, to permit comparisons on the same scale. In addition, no obvious patterns were seen in plots of residuals versus predicted values nor in the leverage plots of residuals versus the individual predictor variables. As a consequence, there appeared to be no benefit in using any transformation, such as the logarithmic transformation of this outcome variable.

The Workers' Compensation Board of Ontario considers a hearing loss of 25 dBHL as an average over the frequencies 0.5, 1, 2 and 3 kHz in noise exposed workers, a compensable disability.[1] Human speech falls within this frequency range and thus, hearing loss in this range constitutes a serious handicap. Individuals with hearing losses only at higher frequencies are generally unaware of the deficit, as the ability to understand normal speech is not substantially affected. This is the case with early noise-induced hearing loss, which occurs initially at 4 to 6 kHz. Nevertheless, these high frequency losses are important to identify as they tend to be progressive,

particularly if noise exposures continue. Generally, at any frequency, a hearing loss can be defined as a loss of 25 dBHL or greater.

The overall arithmetic mean hearing loss for all subjects was less than 25 dBHL at all frequencies except 6 and 8 kHz (Table 4-3). It should be noted that the variability in measured hearing loss is large. The reported standard deviations of arithmetic mean losses were similar in magnitude to the arithmetic means (Table 4-3). Geometric standard deviations ranged from 3.3 to 10.0. This was expected, because of the broad range of expected hearing loss predicted by the various models discussed in Section 2.5.1.

Figure 4-8 (page 115) displays the proportion of subjects with hearing loss greater than 25 dBHL at frequencies of 3 kHz and above, with proportions ranging from 0.20 to 0.43. However, in the lower frequencies, 0.5 to 2 kHz, the proportion of subjects with losses greater than 25 dBHL was 0.10 or less. Thus, few of the subjects were found to have potentially compensable hearing losses. This was expected since individuals with a compensable loss would be less likely to remain in industrial employment. In addition, the average age of the subjects was 37. Given the same level of noise exposure and the progressive nature of hearing loss, an increased number of these subjects might be expected to have a compensable loss as they age.

The three key predictor variables: age, noise and styrene exposure were found to be highly correlated, particularly the two exposure variables. Consequently, findings from regression analyses not including all three variables, or from nonparametric analyses which consider these variables separately, must be interpreted with caution. Both simple linear regression and nonparametric analyses suggested that both noise exposure and styrene exposure were significantly associated with hearing loss. However, when all the variables are included in multiple regression analyses, it became apparent that the association was with noise, rather than styrene, based on both statistical significance as well as on examination of the styrene estimates. The slope estimates (β) for styrene decreased substantially when noise was included in the model, while the standard errors remained essentially unchanged.

5.3.1 Age

The importance of the association between advancing age and the development of hearing loss is well recognized and has again been conclusively demonstrated in this study. The influence of age on the hearing loss pattern is graphically displayed in Figure 4-9 (page 116). As a variable in the multiple regression analyses, age was a significant contributor at all frequencies. The importance of this variable was not diminished when older subjects (age>50) were excluded from the analyses, illustrating that age-related hearing loss also occurs in younger individuals in their thirties and forties. Similarly, when subjects with a substantial hearing loss were

excluded, the age variable remained highly significant, further emphasizing its importance in early hearing loss. The importance of age was undiminished by using the '*Worst*' hearing loss, rather than '*best*', or by considering overall time-weighted average values for the noise and styrene exposures rather than the cumulative or lifetime measures. The time-weighted average value for the lifetime exposures is useful in that it eliminates duration of exposure, which is highly correlated with age. Logistic regression analysis consistently identified age as an important contributor to hearing loss, defined variably as a loss greater than 20 dB to a loss greater than 40 dB.

5.3.2 Noise Exposure

The strong causal relationship between noise exposure and hearing loss is also well documented.[81,93,101] Using multiple linear regression, the association between noise exposure, based on the developed lifetime noise dose estimate, and hearing loss, was generally significant, although weaker than might have been expected. For example, using the age less than 50 dataset, the significance levels ranged from 0.01 to 0.13 for the left and right ears separately from 3 to 8 kHz (Table 4-22A). In Tables 4-26A and B the trend of increasing hearing loss with higher noise exposures can also be seen. Generally, the association between the lifetime occupational noise exposure and hearing loss was strongest at 4 and 3 kHz, especially when using a time-weighted average measure of dose. This is consistent with early noise-induced

hearing loss. Interestingly, logistic regression analyses identified noise exposure as a highly significant contributor to hearing loss at 4 kHz, with hearing loss defined as either a loss greater than 20 or 25 dBHL. Further, the slopes of the audiogram curves between 3 and 4 kHz (Table 4-35) were also consistent with characteristic noise-induced hearing loss (Figure 2-2, page 36). As discussed more fully in Section 5.5, it is likely that a stronger relationship between noise exposure and hearing loss was not seen because of the difficulty in accurately determining retrospective noise exposures. In addition, the large variability in the hearing loss data would reduce the ability of this study, with this sample size, to clearly identify associations.

The significant interaction between age and noise exposure demonstrated that the detrimental effect of noise exposure on hearing loss is increased or strengthened with increased age. Thus, older workers appear to be more sensitive to noise exposure than do younger workers. Noise exposure appears to affect hearing only after a certain age, generally the mid-twenties (Tables 4-24, 4-25). This finding confirms that the permanent effects of noise exposure on hearing occur only after several years of exposure.

5.3.3 Styrene Exposure

There appeared to be no significant relationship between styrene exposure and

hearing loss, in the range of styrene exposures encountered in this study. In a few analyses, the styrene lifetime exposure variable approached statistical significance in the model. Specifically, using the data subset with both age and hearing loss exclusions, that is excluding older subjects and those with substantial hearing loss, styrene exposure approached significance for hearing loss in the left ear only at both 6 and 4 kHz (Table 4-23A). With the same data subset, the time-weighted average styrene exposure was a significant contributor at 6 kHz and approached significance at 3 and 4 kHz, again only in the left ear. Further, a significant negative relationship was found between the slope of the audiograms from 6 to 8 kHz in the left ear and styrene exposure, suggesting that styrene had a greater effect at 6 kHz than at 8 kHz. These findings did not p ,vide strong evidence of an association between styrene exposure and hearing loss.

The styrene lifetime exposure measure is likely a more valid measure, than the lifetime noise exposure measure, as discussed in more detail in Section 5.5. Styrene is uncommon in workplaces, except for fibreglass reinforced plastics manufacture and potential exposures are relatively easily identified from work histories. Therefore, the estimates of duration, as years of exposure, and the periods of no exposure are reasonably accurate. Thus more confidence can be placed in this styrene exposure variable than in the lifetime noise exposure variable.

Moreover, only the left ear, at 6 and 4 kHz, appeared to be potentially affected by styrene exposure, and not consistently. As discussed in Section 2.5.1, greater hearing losses have been demonstrated in the left ear compared with the right. It has been suggested that this may be due to differential noise exposure. Since asymmetry exists for other senses, particularly sight, and other biological factors, such as handedness, the asymmetry in hearing may not be associated with an external specific cause, such as noise exposure. Certainly, differential noise exposures are not likely large and differential styrene exposures are not realistic. Thus it is difficult to explain how styrene might predominantly affect one ear only on the basis of differential exposure. It could be hypothesized that the cause of the hearing sense-asymmetry is also associated with a differential susceptibility to exposure to styrene. This is, however, purely speculative and would require further investigation.

The inability of this study to demonstrate a styrene effect is in direct contrast with the findings of Muijser,[2] described in detail in Section 2.5.4, in which it was suggested that hearing thresholds at 8 kHz were affected by styrene exposure. Table 5-1 provides a comparison, for illustrative purposes, in the left ear, of the hearing threshold data for styrene directly exposed subjects from Muijser with those obtained in the current study. It is interesting to note that the magnitude of hearing loss was statistically significantly higher in the current study, suggesting a correspondingly higher noise exposure. The

degree of variability in both sets of hearing loss data was substantial, as demonstrated by the standard deviations.

Table 5-1: Hearing Loss in Left Ear reported by Muijser[2] and the current study for Directly Exposed Workers

STUDY	Frequency (kHz)			
	3	4	6	8
Muijser (n=30)	10.5 ± 13.1	14.3 ± 14.0	20.3 ± 17.4	9.1 ± 14.6
Current (n=170)	19.9 ± 17.9	21.7 ± 20.1	31.2 ± 20.1	23.7 ± 20.9
student's t	2.75	1.93	2.79	3.67
probability	<0.01	<0.1	<0.01	<0.001

1. Arithmetic Mean (dBHL) ± SD

The age of the subjects was similar, a mean age of 34.6 (SD=8.7) for Muijser's directly exposed subjects compared with 36.0 (SD=11) in the current study. The mean styrene exposures in the Muijser study were somewhat higher then in the current study (Table 5-2).

Table 5-2: Styrene Exposures Reported by Muijser[2] and by the current study

Study	Directly Exposed	Indirectly Exposed
Muijser	138 ± 76[1]	61 ± 32
Current	109 ± 98	36 ± 49

1. Arithmetic mean (mg/m^3) ± SD

Muijser determined personal exposures for each subject over three consecutive days and took a mean value, while the current study involved only one sampling day for each subject. As a consequence, the variability in the data

was lower in the former study.

The major difference between the two studies lies in the treatment of noise exposures. Muijser did not measure noise exposures for each subject. For both his directly and indirectly exposed groups, he reported, based on an unspecified number of instantaneous sound level measurements, background levels of 66 and 70 dB(A) and qualitatively described short duration exposures ranging from 70 to 104 dB(A) arising from occasional use of noisy machinery. The implication is that the exposures for the two groups were uniformly relatively low, and therefore not important in the data analysis. Muijser did not define the term "background" and it should be noted that sound levels of 66 and 70 dB(A) would be typical of an office environment, but highly atypical of a manufacturing/industrial environment during normal operations.

A significant difference was noted in hearing loss at 8 kHz between the directly exposed and the indirectly exposed groups with the mean hearing loss in the left ear being 9.1 and 1.3 dBHL, respectively. It was suggested that this may be due to the styrene exposure. However, no differences in hearing loss were observed between the exposed groups and a control group which was not exposed to styrene. The investigators pointed out that the control group was exposed to considerable levels of background noise, higher than the styrene exposed groups. In addition, it should be noted that the classification

of the subjects into directly exposed or indirectly exposed was based on current jobs and measured styrene exposures and yet the postulated effect is likely chronic.

In the present study, noise exposures were measured for each subject and lifetime exposures estimated from these data and work history. The importance of including this variable in the data analysis was conclusively demonstrated. Regression analyses, modelling either one variable (styrene), or two variables (styrene and age) against hearing loss, indicated that styrene exposure was a statistically significant variable. However, when noise exposure was added to the model, styrene became nonsignificant. Although styrene and noise exposures were found to be highly correlated, there was no large increase in the standard error for the styrene regression coefficient upon incorporation of the noise variable into the model.[151] The conclusions reached by Muijser regarding an effect of styrene might have been considerably different had noise exposures been taken into account. The audiogram patterns reported by Muijser were strongly suggestive of early noise-induced hearing loss, with an increased hearing loss at 4 to 6 kHz and a relative recovery of hearing acuity at 8 kHz (Figure 5-1, page 152). This suggests that the noise exposures were considerably greater than suggested, at least in the past if not currently.

5.3.4 Other Possible Factors

Smoking appeared to be positively associated with hearing loss in the right ear at 6 kHz (Tables 4-22B, 4-23B). In addition, when TWA values were used for styrene and noise exposures, smoking approached significance for hearing loss at 8 kHz (Table 4-26B, 4-27B). These results, although possibly suggestive of a weak relationship, are inconclusive. As discussed above, it is difficult to reconcile a "significant" effect in only one ear.

The association between recreational noise exposures and hearing loss, demonstrated at 6 kHz in the right ear, is again difficult to interpret. Particularly so, since the negative slope estimate would suggest a protective effect. This may be an example of the healthy worker effect, in that individuals who recognize that they have a hearing loss may avoid noisy recreational activities. This again is highly speculative.

Recreational chemical exposure, for example to paints, was not identified as a significant factor in hearing loss, although it approached significance at 3 and 4 kHz with some regression models. There is no reason to believe that these are indicative of an important effect from such exposures. Occupational solvent exposures, other than styrene, also did not appear to be related to hearing loss.

The exposure assignments for recreational noise, chemicals and occupational solvents should be considered, on the whole as rather crude, based on relatively limited questionnaire data. This reduces further the level of importance which might be placed on these findings.

5.3.5 Self-Reported Hearing Acuity

Although the relationship between self-reported hearing acuity and measured hearing level was statistically significant, in practical terms self-reporting is of limited value. The sensitivity of the question was very poor, with only approximately one third of individuals with a hearing loss greater than 25 dBHL, able to recognize this deficit (Table 4-33). Less than 50 percent of those with a loss of greater than 40 dBHL were aware of their loss (Table 4-34). This is not entirely surprising. The frequency range of human speech is generally 0.5 to 3 kHz. Individuals generally only become aware of a deficit in hearing once they have difficulty in understanding speech. Thus, losses above 3 kHz tend to be poorly recognized. It is not surprising that there was a tendancy for improved recognition of hearing loss at the lower frequencies (1 & 2 kHz). For example, although the numbers are small (n=5), 60 percent of those with a loss greater than 40 dBHL at 2 kHz were aware of a deficit. Further, questions seeking information on perceived level of difficulty in hearing under certain situations were also ultimately unreliable in identifying those with a hearing loss, even within the speech frequencies (Table 4-35).

Interestingly, individuals were not only unable reliably to identify if they have a hearing loss, they were also found to have some difficulty in reliably identifying if they had been exposed to high noise levels in the course of their work.(Section 4.3.2, page 76) This is likely a reflection of the subjective nature of the perception of both noise and hearing loss.

5.4 LIMITATIONS AND WEAKNESSES OF THE STUDY

5.4.1 Study Design

Initially a 2 x 2 factorial design was proposed for this study, using the presence or absence of styrene and noise exposure as the two factors. The presence or absence of noise exposure was based on exposures above or below L_{eq} levels of 80 dB(A). Within each of the four exposure groups (Styrene/Noise, Styrene/No-Noise, No-Styrene/Noise, No-Styrene/No-Noise), two sampling strata were included: age and duration of employment (Section 3.1). It was, however, not possible to follow this study design. The number of plants available to the study was more limited than had been expected (Section 3.2) and, as a consequence, insufficient numbers were available to recruit the necessary number of subjects for each of the strata within the four exposure groups. In addition, because of the nature of the plants which were available, insufficient workers who were exposed significantly to styrene but relatively unexposed to noise, were found. As a result, there was a high correlation between styrene and noise exposure. Since noise exposure is

known to cause hearing loss, it is an important confounding exposure. Therefore, a subtle effect of styrene on hearing loss may well have been difficult or impossible to identify in this study.

Several common selection biases have been described in relation to cross-sectional studies.[152] These include selective migration of workers, selective termination of employment and self selection with respect to participation in the study. The bias associated with selective migration of workers from higher to lower exposure areas can be reduced or eliminated through consideration of exposures in both current and all previous jobs or positions. In the present study, for styrene exposure this was accounted for and thus this was not an important source of bias. It is unlikely that workers left employment in this industry as a result of hearing loss, because generally these losses tend to be undetected by workers until later in life, once the magnitude of the loss becomes substantial and reaches the speech frequencies. Thus, bias associated with differential job termination was unlikely. Finally, although several companies refused to cooperate, only 16 of 324 subjects (5 percent) refused to participate, yielding a 95 percent participation rate. Thus, individual subject self-selection did not likely introduce a bias. However, it is possible that the plants which refused to participate may have had higher styrene exposures and different noise exposures. If this were the case, then workers with higher styrene exposures might have been consistently missed from the study.

5.4.2 Study Execution

Studies conducted directly in workplaces are prone to the limitations associated with a lack of full control of the environment and the activities of the subjects. In order to gain entry into a plant and secure cooperation of both management and the workers, the study related activities must create a minimum disruption of plant production or worker schedules. This necessitates a number of compromises which may affect the precision and accuracy of the data. In particular, the hearing loss measurements by pure tone audiometry are most ideally conducted in an audiometric booth located in an extremely quiet area. The audiometric booth used in the present study was mounted inside a cube van and this was parked at a convenient location at each plant site. Although every effort was made to locate the van as far away as possible from noise sources within and around the plants, the location was not always ideal. Thus, the audiometric data were occasionally potentially compromised to some degree by background noise levels. Interference from background noise would result in an elevated measure of hearing loss. However, in using *Best* HL, the best of the pre- or post-shift measure, the magnitude of this potential bias was diminished. Additionally, it is not possible to conduct high frequency audiometry, above 8 kHz, in a field location, because the sensitivity of the instrumentation requires laboratory conditions. Thus, it was not possible to investigate the high frequency effects found in animal studies.

The personal styrene and noise exposure measurements were taken, for each subject, on one day as a full shift, TWA sample. This sampling was limited to only one day for two reasons: cost (equipment, supplies, technical personnel and laboratory) and plant disruption. These TWA exposure measurements, taken as averages over job categories and plants, were used to estimate current job exposure as well as lifetime exposure indices. The weaknesses with these estimates are discussed below. As workplace exposures may vary considerably from day to day, reliance on a single measurement introduces an additional source of imprecision. Exposure measurements taken over several days, accounting for general day to day differences as well as seasonal variations, would provide more precise estimates. Unfortunately this approach is rarely practical or even feasible.

As described previously (Section 5.1), the TWA styrene exposures found during this study were relatively low in comparison to previous studies. This is likely partially due to improved control of styrene exposures in some of the workplaces. In addition, a potential source of workers with higher styrene exposures, namely the fibreglass boat building industry, essentially no longer exists in Ontario because of the economy. Thus, if styrene does contribute to hearing loss, the inability of this study to demonstrate a styrene effect may have been a consequence of the unavailability of subjects with the higher exposures.

Given the known ototoxic effects of certain drugs, individuals currently taking such medication were excluded from the study. However, it was not possible to reliably identify subjects who had previously taken these drugs, particularly antibiotics. Thus, a potential bias may have been introduced. Further, alcohol consumption was also not considered in this study. There is no direct evidence suggesting a causal relationship between alcohol intake and hearing loss, although alcohol clearly affects the CNS. The overall findings of this study however, are not likely to have been influenced by the inclusion of these two variables, because of their magnitude relative to age and noise exposure.

5.5 Limitations of Retrospective Exposure Indices

Retrospective occupational epidemiologic studies rarely have access to high quality quantitative exposure data. Often there is a complete lack of any qualitative or quantitative exposure data. Investigators often are unable to identify a specific causative agent using as the exposure measure, employment in a particular industry. Typically, reliance is placed on a variety of exposure surrogates, such as job titles, duration of employment and proximity to a source of contamination. These are often gleaned from personnel records, questionnaire responses or interviews with the subjects or, in some cases, next of kin. Recognizing the severe limitations introduced by such exposure 'measures', some investigators have used a combination of job title and duration together with semi quantitative estimates of exposure levels, based on the judgements of individuals with substantial knowledge of workplaces and quantitative

exposures, such as occupational hygienists.[153-155]

This study provided a unique opportun'ty to evaluate the validity of various exposure estimates. It is well documented that exposure to noise increases the risk of hearing loss. Considering the noise levels encountered in the fibreglass plants, a relationship between noise exposure and hearing loss was expected. As described in Section 4.3.1 (page 71), lifetime or cumulative noise and styrene exposure indices were calculated, in a conventional manner, using the measured exposure, corrected for protective equipment use, job titles and durations. The results of multiple regression analyses, using these indices, indicated that both age and styrene exposures were significant contributors to hearing loss, while noise exposure was unimportant. Had the study been examining the effects on hearing loss of two exposures, the results of which were unknown for both, the ultimately erroneous conclusion might well have been made that one, styrene, has an important effect, while the other, noise, does not. In this case, however, the inability to demonstrate a noise exposure effect raised serious concerns regarding the validity of the exposure indices.

An alternative approach, equally conventional, involves the use of self reported exposure assessment, based on questionnaire responses. Subjects had provided responses to questions regarding noise exposures in current and previous jobs. A noise exposure index was developed from these responses (Section 4.3.2, page 75). The multiple regression analyses using a noise exposure index based on this self

reported estimate was equally unsuccessful in demonstrating a noise effect. Since noise exposures had been measured for each subject, these could be compared with the individual responses for the current jobs. Questionnaire responses were found to be of limited value in predicting current noise exposures (Table 4-16A,B&C). This clearly has important implications for the use of questionnaire responses or self assessment of occupational noise exposures.

A significant relationship between noise exposure and hearing loss was demonstrated only when noise exposure estimates were based on a semi-quantitative reassessment, by occupational hygienists, of the estimated noise levels for each job category, combined with duration of exposure (see Section 4.3.3, page 78). It would appear, in this instance, that experienced individuals provided more reliable and consistent estimates of noise exposure, than did individual workers. The use of an *expert rating* to assess noise exposures, based on descriptions of jobs and workplaces, should be carried out completely blind to the hearing status of each subject in order to eliminate bias. In this case, the ratings were carried out by the same individuals who conducted the audiometric tests, although the test results were kept separately. Due to the large number of subjects, there is virtually no likelihood of bias having been introduced from this source.

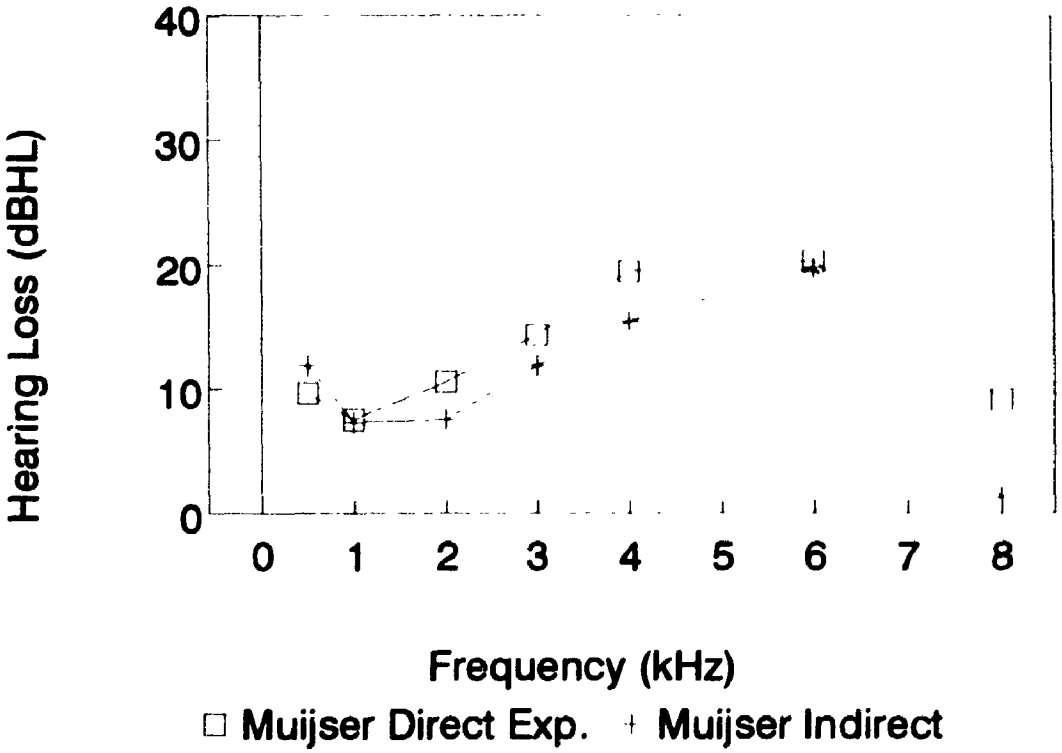
These difficulties encountered with the estimation of lifetime cumulative noise exposure arose from several important factors. Noise, unlike many occupational

hazards, is essentially ubiquitous, with exposure levels varying considerably. In the initial determination of lifetime exposure, all previous jobs, which were unrelated to fibre reinforced plastics manufacture, were assigned a low noise exposure, 80 dB(A). This is clearly incorrect. Self-reported exposures are subject to recall bias, which may be either systematic or random. Systematic biases are often identified in subjects who are aware of their exposure status in the study. Random biases occur for example because of errors in recall. In addition, in this case, the subjects were asked to indicate if the noise exposure was *excessive*, necessitating a subjective judgement to be made, introducing additional bias. The net effect of these biases was to reduce severely the precision and accuracy of the overall exposure estimate, as was demonstrated.

The styrene lifetime or cumulative exposure index cannot be validated to the same extent, since it is the effects of styrene which were unknown and under study. However, styrene is a relatively uncommon occupational hazard, found almost exclusively in the fibreglass industry. Thus, for jobs outside of this industry, a high degree of confidence can be placed in assigning zero styrene exposure. In addition, since styrene has a peculiar and identifiable odour, subjects are more likely to be able to confirm if they have been exposed to this chemical or not. There is no *a priori* reason to expect recall biases, particularly with respect to previous jobs and duration of employment to be different for different occupational hazards.

Finally, all exposure indices using current, measured exposures as a basis for the assignment of exposure levels for previous positions or jobs introduces a potential major bias or error. Over time, exposures to specific hazards in the workplace generally decrease. For example, an overall reduction in styrene exposures was demonstrated in the Dutch fibreglass industry from 1955 to 1988.[148] Many factors influence these decreased exposures, including: increased concern and knowledge regarding the hazard and its toxicological effects, more stringent occupational standards, and improved control technology in the workplace. Therefore, using the current exposures as the basis for assigning exposure magnitudes results in potential underestimation of exposures in the past. As a consequence, particularly in older workers, the overall lifetime exposure would be underestimated, likely affecting the ability to detect associations between exposures and effects. In theory this could be accounted for, if the time course of the decline in exposures were known. However, the time course varies substantially with the nature of the contaminant and by workplace conditions. At best, only rudimentary estimates can be expected. Little would be gained by substituting one uncertainty for another.

Figure 5–1: Left Ear Hearing Loss
Muijser Data



CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

No acute changes in hearing status over the workshift could be attributed to the styrene exposure levels encountered in this study. The competing potential influences from *temporary threshold shifts (TTS)* and the *learning effect* may have prevented a small effect from being observed. Older workers were found to have a greater change in hearing acuity over shift, while those individuals with greater baseline (or pre-shift) hearing loss had smaller changes over shift.

There was also no evidence found in this study of a causal relationship between chronic, long term styrene exposure and the prevalence of hearing loss. As expected, age and noise exposures were markedly and positively associated with hearing loss prevalence. An important interaction between age and noise exposure was demonstrated, with the influence of lifetime noise exposure on hearing loss being strengthened with advancing age. A strong correlation was observed between noise and styrene exposure in the study which might naturally be expected in most industrial environments. As a consequence, studies which have not, or do not, account adequately for both exposures cannot be considered as conclusive.

Smoking, recreational noise and chemical exposures and other workplace solvent exposures did not appear to be associated with the prevalence of hearing loss.

However, the exposure assignments for these factors were based on crude questionnaire data, limiting the interpretation of these findings.

Subjects were unable reliably to identify if they had a hearing loss. More important, self-reported exposure information, obtained from questionnaire responses, was also found to be inadequate in describing exposures, particularly for noise. Subjects were even found to be unreliable in identifying "no noise" exposure situations. The strong correlation between current measured noise exposures and the 'expert rated' exposure index used in this study provided some evidence for the validity of this index. The implications of the use of questionnaire responses for constructing retrospective exposure indices are profound.

6.2 Recommendations for Further Study

This study, the first to take account of both stryene and noise exposures, was not successful in demonstrating an ototoxic effect of styrene, at the exposure levels encountered. As described previously, the industry with the history of highest styrene exposures, namely boat building, has been effectively lost due to the economic climate. These workers are therefore no longer available for inclusion in such a study. It would be interesting to determine if higher exposure levels could produce an effect on hearing, large enough to be detected over the effects of age and noise exposure. Eastern European industry might provide a useful site; and, to reduce the effects of noise, a prospective cohort study, with careful use of hearing protection would be needed.

If aromatic solvent exposure does produce an ototoxic effect, the possibility of an important occupational health problem in Canada still exists, since aromatic hydrocarbon exposures, such as to toluene and xylene are widespread. It is important that the ototoxic potential of these materials also be investigated. However, there are major challenges in terms of the appropriate study design, because of the mixture of exposures encountered in most occupational settings where aromatic hydrocarbons are present. Retrospective studies would suffer from serious problems in exposure assignment as identified in the present study. This would be exacerbated by the likelihood of complex solvent exposures. A prospective cohort study would allow for the identification of mixture components and individual quantification of exposures. Reliance on questionnaire responses for exposure determination would be eliminated. In addition, the control of the important confounding effect of workplace noise could be achieved through rigorous use of hearing protection. In such a study, solvent exposures might also be assessed on the basis of biological markers, such as urinary hippuric acid for toluene exposure and methyl hippuric acid for xylene exposure. These biological markers might better reflect true intake or internal exposure to the substance.

APPENDIX I

CONSENT FORM

(actual form on letterhead)

I have been invited to participate in a study being carried out by Prof. A. Sass-Kortsak, Dr. J. Robertson and Dr. P. Corey from the University of Toronto and the University of Western Ontario into the Ototoxicity of Styrene. My participation in this study will involve the following procedures being carried out.

1. I will be asked some questions about my health and about my work history which will take approximately 15 minutes.
2. I will have my hearing tested at the beginning and at the end of my workshift. This test will take approximately 5 minutes.
3. In order to measure my exposure to styrene and other solvents over my workshift, I will wear on my belt, a lightweight sampling pump attached to a tube. The tube will be hung on my collar.
4. In order to assess styrene intake, I will provide a breath sample at the beginning and end of my shift. The breath sample will be analyzed for STYRENE only.
5. In order to measure my noise exposure, I will wear a small integrating unit, again on my belt, with a small microphone which will be attached on the other side of my collar. The microphone and integrating unit in no way records conversation or other noises; rather it measures noise levels to which I am exposed.

The procedures involved are all safe. My involvement in this study is completely voluntary and whether or not I participate will have no effect on my relationship with my employer. All of the information collected from me will be kept confidential by the University of Toronto and the investigators and will not be released, in such a manner that I could be identified, without my signed consent.

The only exception is that airborne styrene exposures and workplace noise exposure levels will be reported to the Joint Health & Safety Committee, at my workplace. I can withdraw from the study at any time.

DATE:_____

NAME: _____

SUBJECT NUMBER: _____

SIGNATURE:_____

SIGNATURE OF WITNESS: _____

==========

I consent to having the results about my hearing obtained in this study released to my own Doctor whose name is:

_____

DATE: _____

SIGNATURE:_____

SIGNATURE OF WITNESS: _____

Appendix II

QUESTIONNAIRE

(Rev: 30/7/91)

NAME: _____

ADDRESS: _____

PHONE: _____

FAMILY PHYSICIAN: _____

SEX: Male Female

DATE OF BIRTH: _____ _____ _____
Year Month Day

COMPANY: _____

UNION MEMBERSHIP: Canadian Autoworkers

Sheetmetal Workers

Machinists

_____

_____

None

Other

_____

A. EMPLOYMENT HISTORY:

A-1. Current Job

What is your current job title?

_____

When did you start working at this job?

Month Year

Number of months of continuous service?

To which chemicals are you exposed at work?

NONE

Styrene

Acetone

Methylene Chloride

Mineral Spirits

Paints

Other, please specify

_____

_____

On average, how many hours per day at work do you wear a respirator?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Organic Vapour Cartridge

Particulate

Combination

Supplied Air

Other

_____

Do you feel you are exposed to excessive noise in your current job?

Yes No

How would you describe the noise? (check as appropriate)

constantly loud

periodically loud

Is there any impact/impulse noise?

Yes No

How would you describe the pitch of the noise?

high pitch

low pitch

combination

Do you participate in a hearing conservation program?

Yes No

Do you wear hearing protection while at work?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Muffs

Plugs

Other

Do you wear headphones and listen to music <u>at work</u>? (i.e. Sony Walkman, or equivalent)

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

Do you use a Sony Walkman (or equivalent) outside of work hours?

Never

Less than 1 hour per week

5 hours per week

10 hours per week

A-2. <u>Previous Employment</u> - Please provide the following information for EACH previous position even if it is with the same company.

Name of Company: _____

Job Title: _____

Period from: _____ **to:** _____
month year month year

Number of months of continuous service?

To which chemicals are you exposed at work?

NONE

Styrene

Acetone

Methylene Chloride

Mineral Spirits

Paints

Other, please specify

_____

_____

On average, how many hours per day at work do you wear a respirator?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Organic Vapour Cartridge

Particulate

Combination

Supplied Air

Other

_____

Did you feel you were exposed to excessive noise in this job?

Yes No

How would you describe the noise? (check as appropriate)

constantly loud

periodically loud

Is there any impact/impulse noise?

Yes No

How would you describe the pitch of the noise?

high pitch

low pitch

combination

Did you participate in a hearing conservation program?

Yes No

Do you wear hearing protection while at work?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Muffs

Plugs

Other

A-3. Next Previous Position - Please provide the following information for EACH previous position, even if it is with the same company.

Name of Company: _____

Job Title: _____

Period from: _____ to: _____
month year month year

Number of months of continuous service?

To which chemicals are you exposed at work?

NONE

Styrene

Acetone

Methylene Chloride

Mineral Spirits

Paints

Other, please specify

_____

_____

On average, how many hours per day at work do you wear a respirator?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Organic Vapour Cartridge

Particulate

Combination

Supplied Air

Other

Did you feel you were exposed to excessive noise in this job?

Yes No

How would you describe the noise? (check as appropriate)

constantly loud

periodically loud

Is there any impact/impulse noise?

Yes No

How would you describe the pitch of the noise?

high pitch

low pitch

combination

Did you participate in a hearing conservation program?

Yes No

Do you wear hearing protection while at work?

Never

Less than ¼ of the time

About ½ of the time

More than 3/4 of the time

Always

What type?

Muffs

Plugs

Other

_____

C. HEARING BACKGROUND

Have you ever had your hearing tested?

Yes No

If yes, how many times?

When was the most recent? _____

If yes, where?

at work

at my doctor's office

at a clinic

elsewhere, specify

_____

What were the results?

normal (no hearing loss)

hearing loss, describe:_____

other, specify:_____

don't remember

Do you <u>think</u> your hearing is normal?

Yes No

Have you ever had any injuries to your ears?

Yes No

If yes, please describe.

Perforated eardrum

Substantial head injury, requiring medical attention

Severe ear infections

Other

Do you have a medical history of any problems with your ears or your hearing?

Yes No

If yes, please describe.

Do any of your family/immediate relatives - parents, brothers, sisters, grandparents have a medical history of ear or hearing problems?

Yes No

If yes, please describe.

For each of the following statement about everyday situations, try to give an estimate from your own experience of whatever difficulty you have in hearing.

	ALWAYS	MORE THAN 3/4 OF THE TIME	LESS THAN 1/4 OF THE TIME	NEVER
Do you have difficulty hearing a conversation with one other person when you're at home?				
Do you have difficulty hearing in group conversation at home?				
At work do you have difficulty hearing in a conversation?				
(If yes) Is this due to your hearing, due to noise at work or a bit of both?				
1. Due to hearing				
2. Due to noise				
3. A bit of both				
Do you have difficulty hearing the TV or radio when the volume is at the "usual" level at home?				
If someone calls at the house can you hear them ring the door-bell or knock on the door?				
Do you find that people fail to speak clearly?				
Do you get buzzing or ringing noises inside your head or ears?				
If so, does this head noise prevent you from getting to sleep?				

	ALWAYS	MORE THAN 3/4 OF THE TIME	LESS THAN 1/4 OF THE TIME	NEVER
AT WORK:				
Do you experience any of the following symptoms:				
drowsiness				
dizziness				
nausea				
headaches				
fatigue				
lack of balance				
AT HOME:				
On weekends or holidays, do you ever experience the following symptoms:				
drowsiness				
dizziness				
nausea				
headaches				
fatigue				
lack of balance				

RECREATIONAL ACTIVITIES:

Currently:

Please indicate whether you currently (within last 2 years) participate in any of the following activities:

NOTE: Often is approximately once per week or greater. Occasionally is approximately once per month.

ACTIVITY	NEVER	# DAYS/YR
Hunting		
Target Shooting		
Snowmobiling, Motorcycling		
Cross-Country or Downhill Skiing		
Scuba Diving		
Playing in a band (rock, country, etc.)		
Going to rock concerts, disco bars		
Carpentry		
Painting (working with paints,lacquers,thinners)		
Working with glues		
Photography (darkroom work)		
Wearing headphones (Sony Walkman, or equivalent)		

If not mentioned above, please list any hobbies, including military service you do which might get noise or chemical exposures. Indicate frequency (often, occasionally)

Past History:

ACTIVITY	NEVER	# DAYS/YR	HOW LONG AGO?	HOW LONG?	FOR
Hunting					
Target Shooting					
Snowmobiling, Motorcycling					
Cross-Country or Downhill Skiing					
Scuba Diving					
Playing in a band (rock, country, etc.)					
Going to rock concerts, disco bars					
Carpentry					
Painting (working with paints, lacquers,thinners)					
Working with glues					
Photography (darkroom work)					
Wearing headphones (Sony Walkman, or equivalent)					

If not mentioned above, please list any hobbies you do which might get noise or chemical exposures. Indicate frequency (often, occasionally)

==========

SMOKING HISTORY:

Are you a current smoker? Yes No

If no, have you ever smoked? Yes No

If yes, - Cigarettes:

Number per day

How many years

- Cigars: Number per day

How many years

- Pipe: Number per day

How many years

APPENDIX III

DERIVATION OF SOUND INTENSITY - LIFETIME EXPOSURE INDEX

Noise exposure was measured, over one shift, as an equivalent sound level, L_{eq}. An L_{eq} is defined as a steady state sound level which over the measured time period is equivalent to the actual variable sound level, in terms of sound energy. Essentially, an L_{eq} represents a *time-weighted average* energy exposure. It is expressed in decibels.

Sound Intensity, I, is defined as the average rate at which sound energy is transmitted from a source, per unit area, in units of watts per squared meter (W/m^2). Sound intensity is proportional to the square of the sound pressure, $I \propto p^2$. Both sound intensity and sound pressure can be expressed as a decibel, such that:

$$\text{Sound Intensity Level, } L_I = 10 \log_{10} [\, I/I_o \,]$$

where: I = Intensity, W/m^2

I_o = Standard Reference Intensity = 10^{-12} W/m^2

$$\text{Sound Pressure Level, } L_p = 10 \log_{10} [\, p/p_o \,]^2$$

where: p = sound pressure, Pascals

p_o = Standard Reference Pressure = 0.000020 Pascals

As a consequence of the values of the standard reference pressure and intensity, the sound intensity level, L_I, is numerically equal to the sound pressure level, in this case,

L_{eq}. Hearing loss is a function of the total sound energy impinging upon the ear. Sound intensity is the sound energy impacting on, in this case, the ear.

Given:	$L_I = 10 \log_{10} [I/I_o]$
and since:	$L_I = L_{eq}$
Then:	$L_{eq} = 10 \log_{10} [I/I_o]$
Therefore:	$I = 10^{(Leq/10 - 12)}$ watts/m^2

Given the assumption that the area of the eardrum surface is the same for all subjects, then, I is proportional to the total energy per unit time impinging on the ear.

Lifetime exposure was therefore determined by:

$$\sum [10^{(Leq - HP)/10 - 12}] \times \text{Duration}$$

for each job

(where HP = hearing protection use, see page 72)

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